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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia from the 64th American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations from ASH 2022 • December 10-13, 2022 • New Orleans, Louisiana

Special Reporting on:

- Combination of Ibrutinib Plus Venetoclax with MRD-Driven Duration of Treatment Results in a Higher Rate of MRD Negativity in IGHV Unmutated Than Mutated CLL: Updated Interim Analysis of the FLAIR Study
- Residual Disease Kinetics Among Patients with High-Risk Factors Treated with First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): the GLOW Study
- Treatment Outcomes after Undetectable MRD with First-Line Ibrutinib Plus Venetoclax: Fixed Duration (Placebo) Treatment Versus Continued Ibrutinib with Up to 5 Years Median Follow-up in the CAPTIVATE Study
- Final Analysis of the Prospective Multicenter CLL2-GIVe Trial of Obinutuzumab (GA101), Ibrutinib, and Venetoclax in Untreated Patients with CLL with 17p Deletion/TP53 Mutation
- Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease
- Contribution of Obinutuzumab to Acalabrutinib Therapy in Patients with Treatment-Naive CLL: Analysis of Survival Outcomes By Genomic Features
- Zanubrutinib Demonstrates Superior Progression-Free Survival Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Results from Final Analysis of the ALPINE Randomized Phase 3 Study
- MRD4 Eradication at 6 Months and Early Clearance of MRD with Combination of Ibrutinib Plus Venetoclax Results in Sustained Clinical and MRD Responses: Exploratory Analysis of the Blood Cancer UK TAP CLARITY Study
- Phase 1/2 Study of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Results with >4 Years of Follow-up
- Efficacy of Pirtobrutinib in Relapsed/Refractory CLL and Richter Transformation: Additional Results From the Phase 1/2 BRUIN Study
- Initial Results from a Phase 1/2 Dose Escalation and Expansion Study Evaluating MS-553, a Novel and Selective PKCβ Inhibitor, in Patients with CLL/SLL

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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IN RELAPSED/ REFRACTORY CLL

LOW RATES OF ATRIAL FIBRILLATION, HYPERTENSION, AND MAJOR BLEEDING EVENTS[1,2]

ELEVATE-RR: The first Phase 3 head-to-head trial of CALQUENCE vs ibrutinib in R/R CLL[1]

ELEVATE-RR was a randomized, multicenter, open-label, Phase 3 trial of CALQUENCE vs ibrutinib in 533 patients with relapsed/refractory CLL with the presence of 17p deletion and/or 11q deletion. Patients were randomized 1:1 to receive either CALQUENCE 100 mg orally approximately every 12 hours (n=268) or ibrutinib 420 mg orally once daily (n=265) until disease progression or unacceptable toxicity. The primary endpoint was IRC-assessed PFS (non-inferiority*; tested after ~250 events). Secondary endpoints included incidence of any grade atrial fibrillation, incidence of Grade ≥3 infections, incidence of Richter's transformation, and OS.[1]

Common adverse events[1]

- At 40.9-month median follow-up, the most common AEs of any grade (≥20%) in patients receiving CALQUENCE were infections (78%), bleeding (38%), diarrhea (35%), headache (35%), cough (29%), cardiac events (24%), pyrexia (23%), anemia (22%), neutropenia (21%), and fatigue (20%)[1]
- Median duration of exposure: 38.3 months (range: 0.3-55.9) in the CALQUENCE arm; 35.5 months (range: 0.2-57.7) in the ibrutinib arm[1]

Select events of clinical interest at 40.9-month median follow-up[1]

	CALQUENCE (n=266)		ibrutinib (n=263)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
CARDIOVASCULAR EVENTS				
Cardiac events	24	9	30	10
Atrial fibrillation†	9‡	4.9	16‡	3.8
Ventricular arrhythmias§	0	0	1.1	0.4
Bleeding events	38	3.8	51	4.6
Major bleeding events‖	4.5	3.8	5	4.6
Hypertension¶	9	4.1	23	9
OTHER				
Infections#	78	31‡	81	30‡
Interstitial lung disease/pneumonitis	2.6	0.4	7	0.8
Second primary malignancies, excluding non-melanoma skin cancers	9	6	8	5

- Any grade cardiac arrhythmias of unspecified origin were reported including tachycardia (2.6%), arrhythmia (0.8%), and extrasystoles (0.8%) for CALQUENCE; tachycardia (2.7%), arrhythmia (0.8%), and extrasystoles (0.4%) for ibrutinib[1]

*Derivation of the non-inferiority margin (upper bound of HR two-sided 95% CI <1.429) was based on the results of one ibrutinib study. Therefore, it may be difficult to verify the constancy assumption of the historical control.[1]
†Defined as the preferred terms atrial fibrillation and atrial flutter.[1]
‡Select secondary endpoint.[1]
§Includes events with preferred terms: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation.[1]
‖Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).[1]
¶Defined as the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.[1]
#Most common Grade ≥3 infections were pneumonia (CALQUENCE, 10.5%; ibrutinib, 8.7%), sepsis (CALQUENCE, 1.5%; ibrutinib, 2.7%), and urinary tract infection (CALQUENCE, 1.1%; ibrutinib, 2.3%).[1]

The ELEVATE-RR data have not been reviewed by the FDA and are not included in the prescribing information for CALQUENCE.

ASCEND: The first study of a BTKi vs IdR or BR in R/R CLL[2]

ASCEND was a Phase 3, open-label, randomized, multicenter trial in 310 patients with relapsed/refractory CLL. Patients received either CALQUENCE monotherapy 100 mg orally approximately every 12 hours until disease progression or unacceptable toxicity (n=155), or investigator's choice of IdR or BR (n=155). Primary endpoint at the interim analysis (median follow-up of 16.1 months) was IRC-assessed PFS. After the interim analysis at 16.1-month median follow-up, PFS was INV-assessed only. Select secondary endpoints were ORR, OS, and safety.[2,3]

Common adverse events[2]

- **At 46.5-month median follow-up,** the most common adverse events (≥20%) of any grade in patients receiving CALQUENCE were infection (68%), hemorrhage (31%), neutropenia (24%), headache (23%), and diarrhea (21%)[2]
  - The median duration of CALQUENCE exposure was 44.2 months (range:1.1-54.2)[2]
- **At 16.1-month median follow-up,** the most common adverse reactions (≥20%) of any grade in patients receiving CALQUENCE were infection (56%), neutropenia (48%), anemia (47%), thrombocytopenia (33%), lymphocytosis (26%), and headache (22%)[3]
  - Events of clinical interest (any grade; Grade ≥3) included infection (56%; 15%), bleeding (26%; 1.9%), atrial fibrillation (5%; 1.3%), and hypertension (3.2%; 1.9%)[3,4]
  - The median duration of CALQUENCE exposure was 15.7 months (range: 1.1-22.4)[3,4]

Events of clinical interest at 46.5-month median follow-up[2]

	CALQUENCE (n=154)		IdR (n=118)		BR (n=35)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
CARDIOVASCULAR EVENTS						
Atrial fibrillation	8	1.3	3.3	0.8	2.9	2.9
Hemorrhage	31	2.6	8	2.6	6	2.9
Major hemorrhage*	3.2	2.6	2.6	2.6	2.9	2.9
Hypertension	8	4.5	6	0.8	0	0
OTHER						
Infections	68	29	73	34	49	11
Second primary malignancy excluding non-melanoma skin carcinomas	7	6	1.7	0.8	2.9	2.9
Tumor lysis syndrome	0.6	0.6	0.8	0.8	0	0

*Major hemorrhage was defined as any serious or grade ≥3 hemorrhage or central nervous system hemorrhage of any grade.[2]

AEs=adverse events; BR=bendamustine + rituximab; BTKi=Bruton tyrosine kinase inhibitor; CLL=chronic lymphocytic leukemia; IdR=idelalisib + rituximab; INV=investigator; IRC=Independent Review Committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory.

CALQUENCE tablets can be taken with any acid-reducing agent, including proton pump inhibitors, antacids, and H2-receptor antagonists[3]

To learn more about the tablet formulation visit calquencehcp.com/tablet

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets

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.

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.

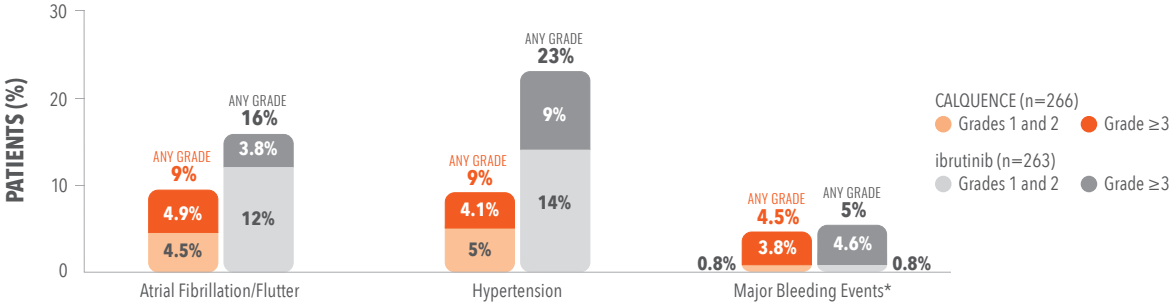
Atrial Fibrillation and Flutter

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 (eg, palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

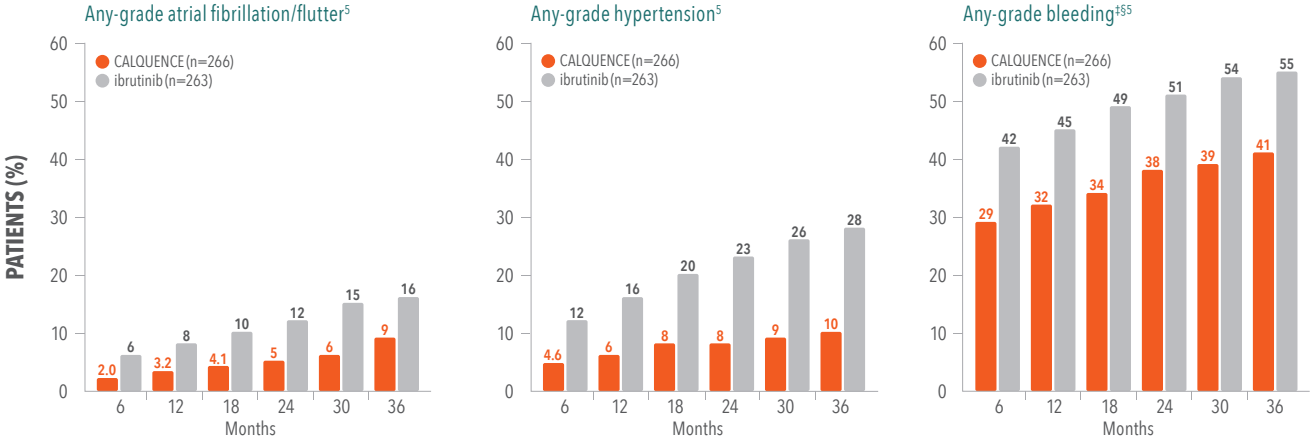
VIEW HEAD-TO-HEAD TRIAL RESULTS

CALQUENCE®
acalabrutinib 100 mg tablets

ELEVATE-RR: Select AEs with CALQUENCE and ibrutinib at 40.9-month median follow-up[1]



ELEVATE-RR: Post hoc analysis of cumulative incidence of select AEs of clinical interest†[5]



- Overall incidence rates of bleeding (any grade, Grade ≥3): CALQUENCE (38%, 3.8%), ibrutinib (51%, 4.6%)[1]

*Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or that was a central nervous system hemorrhage (any severity grade).[1]
†Investigator-selected cumulative incidences of events of clinical interest and common adverse events were assessed using Kaplan-Meier methods and a Cox proportional-hazards model.[1,5]
‡Includes multiple adverse event terms including major bleeding, which was defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or that was a central nervous system hemorrhage (any grade).[5]
§Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis.[5]

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

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

*Treatment-emergent decreases (all grades) of hemoglobin, platelets, and neutrophils were based on laboratory measurements and adverse reactions.

In patients with previously untreated CLL exposed to CALQUENCE, 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 plus obinutuzumab arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (7% and 2.8%, respectively).

Adverse reactions led to CALQUENCE dose reduction in 7% and 4% of patients in the CALQUENCE plus obinutuzumab arm (N=178) and CALQUENCE monotherapy arm (N=179), respectively. Adverse events led to discontinuation in 11% and 10% of patients, respectively. Increases in creatinine to 1.5 to 3 times the upper limit of normal (ULN) occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

In patients with relapsed/refractory CLL exposed to CALQUENCE, 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.

Adverse reactions led to CALQUENCE dose reduction in 3.9% of patients (N=154), dose interruptions in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and discontinuation in 10% of patients, most frequently due to second primary malignancies followed by infection. Increases in creatinine to 1.5 to 3 times ULN occurred in 1.3% of patients who received CALQUENCE.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid co-administration of CALQUENCE with a strong CYP3A inhibitor. If these inhibitors will be used short-term, interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE.

Moderate CYP3A Inhibitors: Reduce the dosage of CALQUENCE to 100 mg once daily when co-administered with a moderate CYP3A inhibitor.

Strong CYP3A Inducers: Avoid co-administration of CALQUENCE with a strong CYP3A inducer. If co-administration is unavoidable, increase the dosage of CALQUENCE to 200 mg approximately every 12 hours.

SPECIFIC POPULATIONS

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. Advise pregnant women of the potential risk to a fetus.

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 1 week following the last dose of CALQUENCE.

It is not known if CALQUENCE is present in human milk. Advise lactating women not to breastfeed while taking CALQUENCE and for 2 weeks after the last dose.

Avoid use of CALQUENCE in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

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

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, call 1-800-FDA-1088.

References: 1. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441-3452 and supplementary appendix. **2.** Jurczak W, Pluta A, Wach M, et al. Acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia: ASCEND results at ~4 years of follow-up. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022. Abs 7538. **3.** CALQUENCE® (acalabrutinib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022. **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. *J Clin Oncol*. 2020;38(25):2849-2861 and supplementary appendix. **5.** Seymour JF, Byrd JC, Hillmen P, et al. Characterization of Bruton tyrosine kinase inhibitor (BTKi)-related adverse events in a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia (CLL). Poster presented at the American Society of Hematology (ASH) Annual Meeting; December 11-14, 2021. Abs 3721.

AstraZeneca

CALQUENCE®
acalabrutinib 100 mg tablets

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

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

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

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

Advise patients to swallow tablet whole with water. Advise patients not to chew, crush, dissolve, or cut the tablets. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

Recommended Dosage for Drug Interactions

Dosage Modifications for Use with CYP3A Inhibitors or Inducers
These are described in Table 1 *[see Drug Interactions (7) in the full Prescribing Information]*.

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

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

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

Table 2: Recommended Dosage Modifications for Adverse Reactions

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

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%) *[see Adverse Reactions (6.1) in the full Prescribing Information]*. These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jirovecii* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

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

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

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

Second Primary Malignancies
Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter
Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* Per NCI CTCAE version 4.03
† Includes any adverse reactions involving infection or febrile neutropenia
‡ Includes 3 fatal cases in the CALQUENCE plus obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm and 1 fatal case in the obinutuzumab plus chlorambucil arm

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

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:

- *Neoplasms:* second primary malignancy (10%), non-melanoma skin cancer (5%)
- *Cardiac disorders:* atrial fibrillation or flutter (3.6%), hypertension (5%)
- *Infection:* herpesvirus infection (6%)

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

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

*Per NCI CTCAE version 4.03
[a] Excludes electrolytes

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

ASCEND

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

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

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

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

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

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

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

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

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:

- *Skin and subcutaneous disorders:* bruising (10%), rash (9%)
- *Neoplasms:* second primary malignancy (12%), non-melanoma skin cancer (6%)
- *Musculoskeletal and connective tissue disorders:* arthralgia (8%)
- *Cardiac disorders:* atrial fibrillation or flutter (5%), hypertension (3.2%)
- *Infection:* herpesvirus infection (4.5%)

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

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

Per NCI CTCAE version 5
[a] Excludes electrolytes

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Pregnancy Testing

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

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 1 week following the last dose of CALQUENCE. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

Avoid use of CALQUENCE in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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Combination of Ibrutinib Plus Venetoclax with MRD-Driven Duration of Treatment Results in a Higher Rate of MRD Negativity in IGHV Unmutated Than Mutated CLL: Updated Interim Analysis of the FLAIR Study

The ongoing phase 3 FLAIR study was developed with an adaptive trial design to compare different ibrutinib-based regimens with standard frontline treatment for chronic lymphocytic leukemia (CLL).[1] Initially, the study included 2 arms comparing fludarabine, cyclophosphamide, and rituximab (FCR) vs ibrutinib plus rituximab.[2] The trial design was subsequently adapted in 2017 to add 2 arms: ibrutinib monotherapy as well as ibrutinib in combination with venetoclax. The primary endpoint for the comparison between these 2 newer arms—achievement of minimal residual disease (MRD) negativity—was evaluated during the interim analysis, when 50% of patients reached 2 years postrandomization, and presented at ASH 2022.[3]

The duration of therapy in both arms was determined by MRD status. MRD was assessed in the peripheral blood and bone marrow at 9 months postrandomization; MRD in the peripheral blood was subsequently assessed at 12 months postrandomization and every 6 months thereafter. The first MRD-negative result prompted a repeat analysis 3 months later; if again negative, MRD was assessed in both the peripheral blood and bone marrow 3 months after that. An MRD-negative status in both the peripheral blood and bone marrow rendered the initial MRD-negative status the time to MRD negativity. The planned duration of therapy was calculated as twice the time to MRD negativity. A patient could stop therapy as early as 2 years postrandomization, and patients could restart ibrutinib if they became MRD-positive.

Patients who were 75 years of age or less and with previously untreated CLL requiring therapy by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria were eligible for enrollment. At this interim analysis, the median patient age was 63 years (range, 33-75 years), with 34.3% of patients over the age of 65. A total of 45.3% of patients had unmutated *IGHV*, and 9.1% had subset 2 *IGHV* status (defined by the *IGHV3-21/IGLV3-21* combination with a short variable heavy complementarity-determining region 3 of 9 amino acids[4]).

The combination of ibrutinib plus venetoclax resulted in 65.4% MRD-negative remissions in the bone marrow and 71.3% in the peripheral blood, within 2 years postrandomization. The median time to achieving MRD negativity in the ibrutinib plus venetoclax arm was 19 months in the bone marrow and 12 months in the peripheral blood. A total of 58 of the 136 patients (42.6%) in this arm stopped treatment at month 24 because of MRD negativity.

When assessed by subgroup in an exploratory analysis, the incidence of MRD negativity within 2 years of ibrutinib plus venetoclax treatment was higher in patients with *IGHV*-unmutated than -mutated CLL (79.7% vs 56.4%, respectively). A logistical regression model was used to assess achievement of MRD negativity within 2 years in bone marrow by *IGHV* status for patients treated with ibrutinib plus venetoclax. Patients with *IGHV*-unmutated CLL had a 3.6-fold higher likelihood of achieving MRD negativity in the bone marrow compared with patients with *IGHV*-mutated CLL (95% CI, 1.59-8.15; *P*=.0022). The median time to MRD negativity was also shorter in patients with *IGHV*-mutated disease.

References

1. Collett L, Howard DR, Munir T, et al. Assessment of ibrutinib plus rituximab in front-line CLL (FLAIR trial): study protocol for a phase III randomised controlled trial. *Trials*. 2017;18(1):387.
2. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: results of the phase III NCRI FLAIR trial. *Blood*. 2021;138(Suppl 1):642.
3. Munir T, Pitchford A, Bloor A, et al. Combination of ibrutinib plus venetoclax with MRD-driven duration of treatment results in a higher rate of MRD negativity in IGHV unmutated than mutated CLL: updated interim analysis of FLAIR study [ASH abstract 94]. *Blood*. 2022;140(Suppl 1).
4. Agathangelidis A, Darzentas N, Hadzidimitriou A, et al. Stereotyped B-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies. *Blood*. 2012;119(19):4467-4475.

ABSTRACT SUMMARY Comprehensive Cardiac Testing in Asymptomatic Chronic Lymphocytic Leukemia (CLL) Patients on Ibrutinib

In an ongoing phase 2 study of short-course fludarabine added to continuous ibrutinib in patients with previously untreated CLL, 2 cases of sudden death on study were reported. The investigators hypothesized that systematic screening for arrhythmias could identify individuals at increased risk of cardiac adverse events among otherwise clinically asymptomatic patients on ibrutinib. The authors reported that cardiac screening identified actionable clinical findings in 4 (19%) of the patients evaluated. Of these, 2 patients were able to resume ibrutinib while ibrutinib discontinuation was recommended as a precaution in the other 2 patients.

Reference

Itsara A, Sun C, Inhye E, et al. Comprehensive cardiac testing in asymptomatic chronic lymphocytic leukemia (CLL) patients on ibrutinib [ASH abstract 1813]. *Blood*. 2022;140(Suppl 1).

Residual Disease Kinetics Among Patients with High-Risk Factors Treated with First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): the GLOW Study

The phase 3 GLOW study evaluated a fixed-duration combination regimen of ibrutinib plus venetoclax in older patients and/or patients with comorbidities with previously untreated CLL.[1] In GLOW, compared to chlorambucil plus obinutuzumab, this fixed-duration combination was associated with superior PFS, deeper and more durable undetectable MRD responses, and a reduced requirement for subsequent anticancer treatment. At ASH 2022, a further evaluation of patients in the GLOW study was reported, with a focus on patients with risk factors associated with worse outcomes for both chemoimmunotherapy and venetoclax plus anti-CD20 therapies—namely, unmutated *IGHV*.[2] This current analysis occurred with a median study follow-up of 46 months.

In the overall population, progression-free survival (PFS) by independent review committee remained superior for the combination of ibrutinib plus venetoclax compared with chlorambucil plus obinutuzumab (3.5-year PFS: 74.6% vs 24.8%, respectively; HR 0.214; 95% CI, 0.138-0.334; *P* <.0001). Undetectable MRD was achieved early during the course of treatment with ibrutinib plus venetoclax. Nearly half of patients (46.2%) treated with this combination achieved undetectable MRD after 6 cycles of combined ibrutinib plus venetoclax, reaching up to 54.7% at 3 months after the end of treatment. From there, the rate of undetectable MRD declined by <10% annually, with a 17% decrease over 2 years. At 27 months after the end of treatment, nearly 40% of patients had undetectable MRD. The ibrutinib plus venetoclax combination was associated with superior PFS regardless of MRD status at 3 months after the end of treatment. The PFS rate at 2 years post-treatment remained ≥80% regardless of MRD status.

The 3.5-year PFS rate was also higher for the ibrutinib plus venetoclax combination compared to the chlorambucil plus obinutuzumab combination in patients with either mutated or unmutated *IGHV*. However, patients with mutated *IGHV* achieved prolonged PFS compared to patients with unmutated *IGHV*. Among patients with mutated *IGHV*, the 3.5-year PFS rate was over 90% regardless of MRD status at three months after the end of treatment. In patients with unmutated *IGHV*, the 3.5-year PFS rate was 90% in patients with undetectable MRD, and 67% in patients with detectable MRD at three months after the end of treatment.

Finally, 3.5-year overall survival (OS) was reported, and was higher with ibrutinib plus venetoclax compared with chlorambucil plus obinutuzumab (87.5% vs 77.6%, respectively; HR 0.487; 95% CI, 0.262-0.907; nominal *P* =.0205. Most deaths in the chlorambucil plus obinutuzumab arm occurred while off treatment, and more infection-related deaths were seen with chlorambucil plus obinutuzumab.

References

1. Kater AP, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evid*. 2022;1(7):1-13.
2. Niemann CU, Munir T, Moreno C, et al. Residual disease kinetics among patients with high-risk factors treated with first-line fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O): the Glow study [ASH abstract 93]. *Blood*. 2022;140(Suppl 1).

ABSTRACT SUMMARY NX-2127-001, a First-in-Human Trial of NX-2127, a Bruton's Tyrosine Kinase-Targeted Protein Degrader, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia and B-Cell Malignancies

NX-2127 is a novel agent that results in targeted BTK ubiquitination and proteasomal degradation, and is under investigation for patients with CLL and other B cell malignancies who have disease resistant or refractory to multiple prior therapies. Results from the Phase 1a dose-escalation evaluation of this agent were reported. Of 12 response-evaluable patients with CLL, the best ORR was 33%; the data suggested that the ORR increased with longer follow-up (ORR: 16.7% at 2 months, 42.9% at 4 months, 50% at 6 months). Responses were also observed in BTK/BCL-2 inhibitor double-refractory patients. One dose-limiting toxicity, cognitive impairment, occurred in a patient with CLL at 300 mg. The most common adverse events included fatigue, a decrease in neutrophil count, and anemia.

Reference

Mato AR, Wierda WG, Ai WZ, et al. NX-2127-001, a first-in-human trial of NX-2127, a Bruton's tyrosine kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies [ASH abstract 965]. *Blood*. 2022;140(Suppl 1).

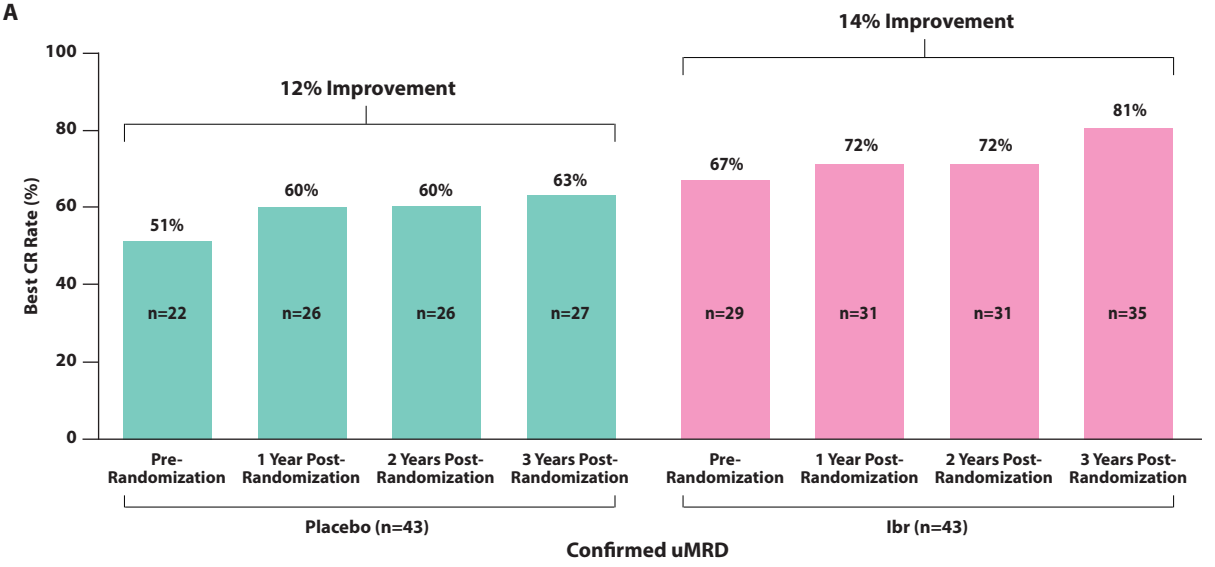
Treatment Outcomes after Undetectable MRD with First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Fixed Duration (Placebo) Treatment Versus Continued Ibr with up to 5 Years Median Follow-up in the CAPTIVATE Study

CAPTIVATE was an international, multicenter phase 2 study designed to evaluate the combination of ibrutinib plus venetoclax as frontline therapy in 2 cohorts of patients: a fixed-duration cohort and an MRD cohort.[1,2] In the MRD cohort, patients with confirmed undetectable MRD following completion of ibrutinib plus venetoclax were randomized in a double-blind manner to receive placebo (ie, a fixed-duration regimen) or continued ibrutinib. At a primary analysis, the 1-year disease-free survival (DFS) rates were similar between these 2 arms (95% vs 100%, respectively; difference, 4.7%; 95% CI, -1.6-10.9; *P*=.15).[3] Results from a longer-term follow-up (median 56 months) were presented at ASH 2022.[4]

In this longer-term follow-up of the MRD cohort, the 3-year DFS rates continued to be similar between the placebo and ibrutinib arms (85% vs 93%, respectively; difference, 8.3%; 95% CI, -5.5-22.1; *P*=.1621). The responses achieved with the ibrutinib plus venetoclax combination proved durable, with no significant difference in duration of complete response (CR) between the placebo and ibrutinib arms (Figure 1A).

The 4-year-free PFS rate was 88% (95% CI, 73.6-94.8) in the placebo arm, compared with 95% (95% CI, 82.3-98.8) with continued ibrutinib. The 4-year OS rates were also similar between the 2 arms (100% vs 98%, respectively). Further, these efficacy

A



B

Efficacy outcomes, % (95% CI)	All treated Placebo (n=43)	All treated Ibrutinib (n=43)	del (17p), TP53 mut, or CK Placebo (n=6)	del (17p), TP53 mut, or CK Ibrutinib (n=20)
DFS (3 year)	85 (69-93)	93 (80-98)	100 (100-100)	95 (70-99)
PFS (4 year)	88 (74-95)	95 (82-99)	100 (100-100)	95 (70-99)
OS (4 year)	100 (100-100)	98 (84-100)	100 (100-100)	100 (100-100)

Figure 1. Complete response rates in the MRD cohort (A) and efficacy outcomes in high-risk patients of the MRD cohort (B) of the CAPTIVATE trial. CK, complex karyotype; CR, complete response; DFS, disease-free survival; Ibr, ibrutinib; MRD, minimal residual disease; uMRD, undetectable MRD; OS, overall survival; PFS progression-free survival. Adapted from Allan JN, et al. ASH abstract 92. *Blood*. 2022;140(suppl 1).

outcomes were analyzed across patient subgroups, including those with del(17p), *TP53* mutation, or a complex karyotype (Figure 1B). Overall, the outcomes among these subgroups were consistent with those observed in the overall MRD cohort.

During the randomized portion of this trial, the incidence of adverse events was small. One new atrial fibrillation event occurred in the ibrutinib arm, and there were no new grade 3 or higher hemorrhage events. The study investigators concluded that these results continued to support a fixed-duration regimen and the potential for durable treatment-free remissions.

References

1. Clinicaltrials.gov. Ibrutinib plus venetoclax in subjects with treatment-naive chronic lymphocytic leukemia /small lymphocytic lymphoma (CLL/SLL). Last updated February 18, 2022. Accessed January 17, 2023. https://clinicaltrials.gov/ct2/show/NCT02910583
2. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. *Blood*. 2022;139(22):3278-3289.
3. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. *J Clin Oncol*. 2021;39(34):3853-3865.
4. Allan JN, Siddiqi T, Kipps TJ, et al. Treatment outcomes after undetectable MRD with first-line ibrutinib (Ibr) plus venetoclax (Ven): fixed duration treatment (placebo) versus continued Ibr with up to 5 years median follow-up in the CAPTIVATE study [ASH abstract 92]. *Blood*. 2022;140(Suppl 1).

Final Analysis of the Prospective Multicenter CLL2-GIVe Trial of Obinutuzumab (GA101, G), Ibrutinib (I), and Venetoclax (Ve) in Untreated Patients with CLL with 17p Deletion/*TP53* Mutation

CLL2-GIVe was an open-label, multicenter phase 2 trial that enrolled patients with previously untreated CLL with del(17p) and/or *TP53* mutation. This study was designed to evaluate time-limited, response-adapted, fixed-duration combination treatment composed of obinutuzumab, ibrutinib, and venetoclax in these high-risk patients. The GIVe regimen consisted of induction therapy (6 cycles of obinutuzumab, ibrutinib, and venetoclax), with venetoclax and ibrutinib continued for up to 6 additional cycles as consolidation therapy. Ibrutinib monotherapy was then administered for cycles 13 to 36 in patients not achieving a CR and with undetectable MRD at cycles 9 and 12. The primary endpoint was CR rate at cycle 15 (final restaging). Initial results from the CLL2-GIVe trial were previously published, showing that the primary endpoint was met with a CR rate of 58.5% at cycle 15 (95% CI, 42.1-73.7; $P<.001$).[1] Final results were presented at ASH 2022.[2]

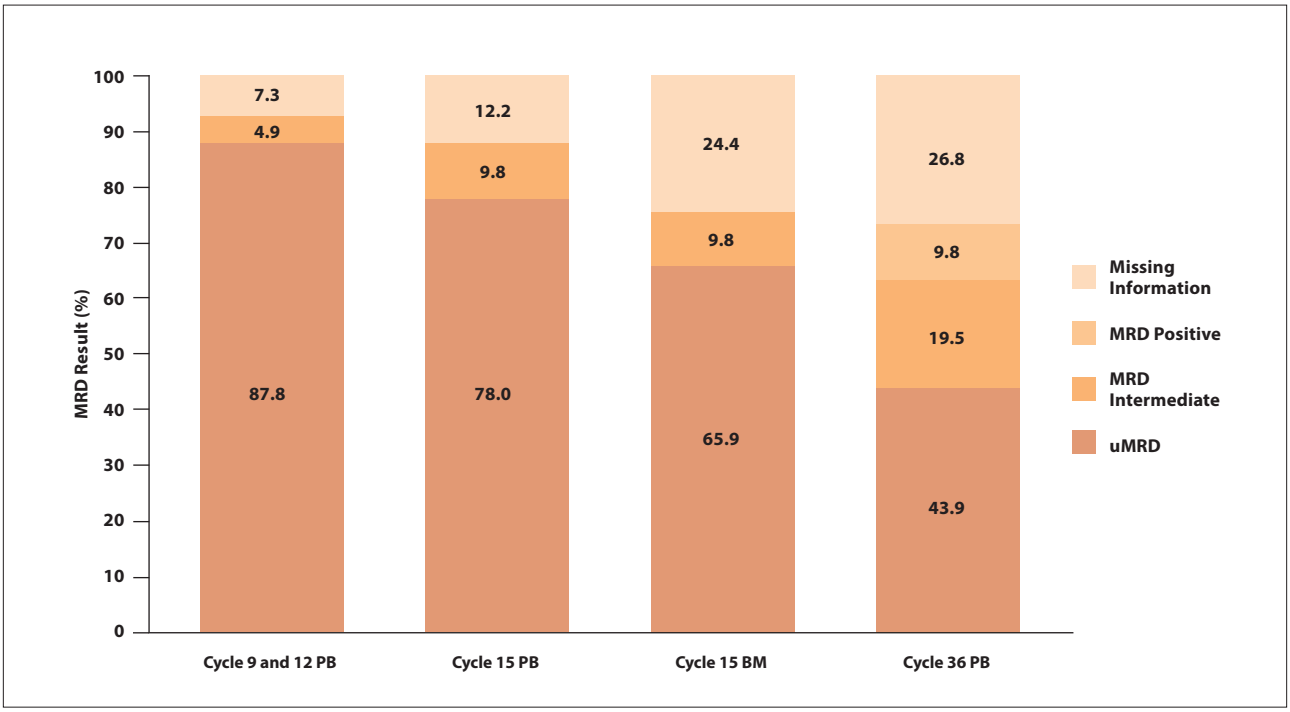


Figure 2. MRD results for patients treated with obinutuzumab, ibrutinib, and venetoclax in the CLL2-GIVe trial. uMRD: $<10^{-4}$; MRD intermediate: 10^{-4} to $<10^{-2}$; MRD positive: $\geq 10^{-2}$. BM, bone marrow; MRD, minimal residual disease; PB, peripheral blood; uMRD, undetectable MRD. Adapted from Huber H, et al. ASH abstract 343. *Blood*. 2022;140(suppl 1).

The median age of patients in the CLL2-GIVe trial was 62 years (range, 35-85 years), and 78.0% had *IGHV*-unmutated disease. Nearly two-thirds of patients (61.6%) had a complex karyotype (3 or more chromosomal aberrations). A total of 58.5% had del(17p) and *TP53* mutation, and 4.9% had del(17p) without *TP53* mutation. One-third of patients (36.6%) had *TP53* mutation with no del(17p).

In this final analysis, the overall response rate (ORR) at cycle 15 was 100%, composed of 58.5% CR/incomplete CR (CRi) (95% CI, 42.1-73.7; *P*<.001) and 41.5% partial responses (PR). MRD results are shown in Figure 2; 87.8% of patients achieved undetectable MRD at cycles 9 and 12. After a median follow-up of 38.4 months, the 3-year PFS rate was 79.9% and the 3-year OS rate was 92.6%. PFS outcomes were impacted by the CLL genetics. For example, the 3-year PFS rate was 100% in patients with no del(17p) and was 67.6% in patients with del(17p) (log-rank *P*=.012). In patients with a complex karyotype, the 3-year PFS was 70.4%, compared with 93.3% in patients without a complex karyotype (log-rank *P*=.215). Finally, the 3-year PFS rate was 74.0% in patients with unmutated *IGHV* compared with 100% in patients with mutated *IGHV* (*P*=.147). However, these analyses were limited to a small patient number.

The incidence of adverse events was highest during the first 6 cycles, then decreased during the course of treatment. Neutropenia (48.8% grade ≥3) and thrombocytopenia (17.1% grade ≥3) were the most common hematologic adverse events reported. The most frequently reported nonhematologic adverse events were infections/infestation, diarrhea, infusion-related reactions, headache, and nausea. The most common infections included respiratory tract infections (33%), gastrointestinal infections (9%), and viral infections (9%), as well as infections with an unspecified pathogen (24%). Atrial fibrillation was reported in 14.6% of patients (2.4% were grade ≥3).

References

1. Huber H, Edenhofer S, von Tresckow J, et al. Obinutuzumab (GA-101), ibrutinib, and venetoclax (GIVe) frontline treatment for high-risk chronic lymphocytic leukemia. *Blood*. 2022;139(9):1318-1329.
2. Huber H, Tausch E, Schneider C, et al. Final analysis of the prospective multicenter CLL2-GIVe trial of obinutuzumab (GA101, G), ibrutinib (I), and venetoclax (Ve) in untreated patients with CLL with 17p deletion/TP53 mutation [ASH abstract 343]. *Blood*. 2022;140(Suppl 1).

Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease

The CLL14 trial demonstrated that venetoclax plus obinutuzumab administered in a time-limited regimen was highly effective as a frontline regimen for CLL.[1] However, this study also showed that responses with this combination were not as durable for patients with *TP53*-mutated disease.[2] The addition of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib to this combination, creating a triplet regimen, has shown efficacy in both all-comer and patients with high-risk disease; however cardiac and infectious adverse

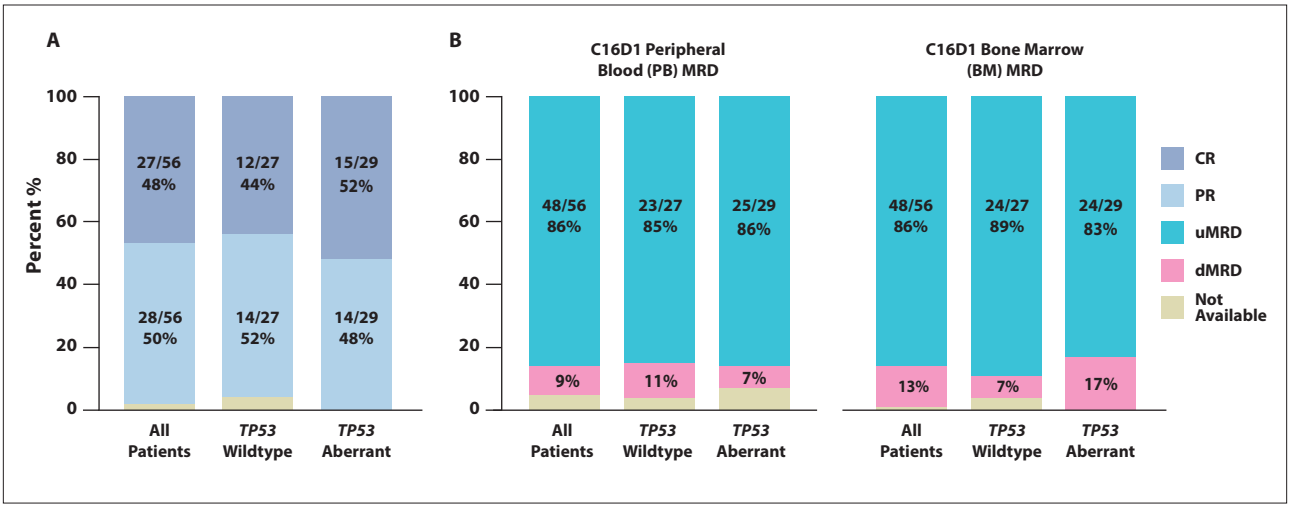


Figure 3. Response rates by iwCLL criteria at cycle 16 (A) and uMRD (10^{-4}) rates (B) in patients treated with acalabrutinib, obinutuzumab, and venetoclax in a phase 2 trial. C16D1, cycle 16 day 1; CR, complete response; dMRD, detectable MRD; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; PR, partial response; uMRD, undetectable MRD. Adapted from Ryan CE, et al. ASH abstract 344. *Blood*. 2022;140(suppl 1).

events were common.[3-5] Because of its lower incidence of these toxicities, the second-generation BTK inhibitor acalabrutinib has also been explored in this triplet regimen (acalabrutinib plus venetoclax and obinutuzumab [AVO]). Results from an initial cohort unrestricted by genetic risk who were treated with this triplet regimen have been previously published.[6] At ASH 2022, results from a different cohort with enrollment restricted to high-risk patients were presented.[7] In addition, results from the initial unrestricted cohort were updated.

The primary endpoint, the rate of CR with undetectable MRD in the bone marrow at cycle 16, was achieved in 43% of the unrestricted cohort and in 45% of the *TP53*-mutated cohort (Figure 3A). An additional 50% and 52% of patients in each cohort, respectively, achieved a PR. Further, in patients in the unrestricted cohort, the AVO triplet regimen was associated with high rates of undetectable MRD at cycle 16 (Figure 3B) both in the peripheral blood (86%) and bone marrow (86%). Similar rates of undetectable MRD at cycle 16 were also reported in the peripheral blood (86%) and bone marrow (83%) of patients with *TP53*-mutated disease. An exploratory analysis showed that these results were durable through cycle 25. At a median follow-up of 35 months, 92.6% of patients remained progression free, and the overall OS rate was 98.5%.

Headache (78%), fatigue (76%), bruising (66%), and nausea (49%) were the most common nonhematologic adverse events reported; neutropenia and thrombocytopenia each occurred in more than 70% of patients. Atrial fibrillation occurred at a rate of 3.0%. There were no major bleeding events and no occurrences of opportunistic infections. Grade 3 non-COVID-19 infections occurred in 5.8% of patients; COVID-19 infections occurred in 9.0% of patients.

The AVO combination is currently under further investigation in the phase 3 ACE-CL-311/AMPLIFY trial in patients with non-high-risk CLL.[8]

References

1. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.
2. Tausch E, Schneider C, Robrecht S, et al. Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. *Blood*. 2020;135(26):2402-2412.
3. Rogers KA, Huang Y, Ruppert AS, et al. Phase II study of combination obinutuzumab, ibrutinib, and venetoclax in treatment-naïve and relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(31):3626-3637.
4. Huber H, Edenhofer S, von Tresckow J, et al. Obinutuzumab (GA-101), ibrutinib, and venetoclax (GIVe) frontline treatment for high-risk chronic lymphocytic leukemia. *Blood*. 2022;139(9):1318-1329.
5. Huber H, Tausch E, Schneider C, et al. Final analysis of the prospective multicenter CLL2-GIVe trial of obinutuzumab (GA101, G), ibrutinib (I), and venetoclax (Ve) in untreated patients with CLL with 17p deletion/TP53 mutation [ASH abstract 343]. *Blood*. 2022;140(Suppl 1).
6. Davids MS, Lampson BL, Tyekucheva S, et al. Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study. *Lancet Oncol*. 2021;22(10):1391-1402.
7. Ryan CE, Lampson BL, Tyekucheva S, et al. Updated results from a multicenter, phase 2 study of acalabrutinib, venetoclax, obinutuzumab (AVO) in a population of previously untreated patients with CLL enriched for high-risk disease [ASH abstract 344]. *Blood*. 2022;140(Suppl 1).
8. Clinicaltrials.gov. Study of acalabrutinib (ACP-196) in combination with venetoclax (ABT-199), with and without obinutuzumab (GA101) versus chemoimmunotherapy for previously untreated CLL. Last updated December 16, 2022. Accessed January 17, 2023. https://clinicaltrials.gov/ct2/show/NCT03836261

Contribution of Obinutuzumab to Acalabrutinib Therapy in Patients with Treatment-Naive CLL: Analysis of Survival Outcomes By Genomic Features

The ELEVATE-TN trial evaluated acalabrutinib, administered as monotherapy or in combination with the anti-CD20 antibody obinutuzumab, as frontline treatment for CLL.[1,2] Significantly improved PFS was observed with the acalabrutinib plus obinutuzumab combination, but a post hoc analysis showed no significant difference in OS between the 2 groups.[3] This combination has also been evaluated in the CL-003 study.[4] In a poster presented at ASH 2022, a post hoc analysis was performed from patients with previously untreated CLL who received either acalabrutinib alone or in combination with obinutuzumab.[5]

A total of 376 patients were included, of whom 260 were considered to have high-risk disease (comprised of 20% with del(17p) and/or *TP53* mutation, 88% with unmutated *IGHV*, and 25% with a complex karyotype).

Among patients with non-high-risk disease, differences in PFS and OS outcomes were not significantly different between the acalabrutinib monotherapy and acalabrutinib plus obinutuzumab groups. In patients with del(17p) and/or *TP53* mutation, or with a complex karyotype, the addition of obinutuzumab to acalabrutinib also did not significantly improve PFS or OS. In contrast, PFS (HR, 0.44; 95% CI, 0.21-0.86; *P*=.02) and OS (HR, 0.34; 95% CI, 0.11-0.89; *P*=.03) were significantly prolonged with the addition of obinutuzumab to acalabrutinib in patients with unmutated *IGHV* (Figure 4).

References

1. 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.

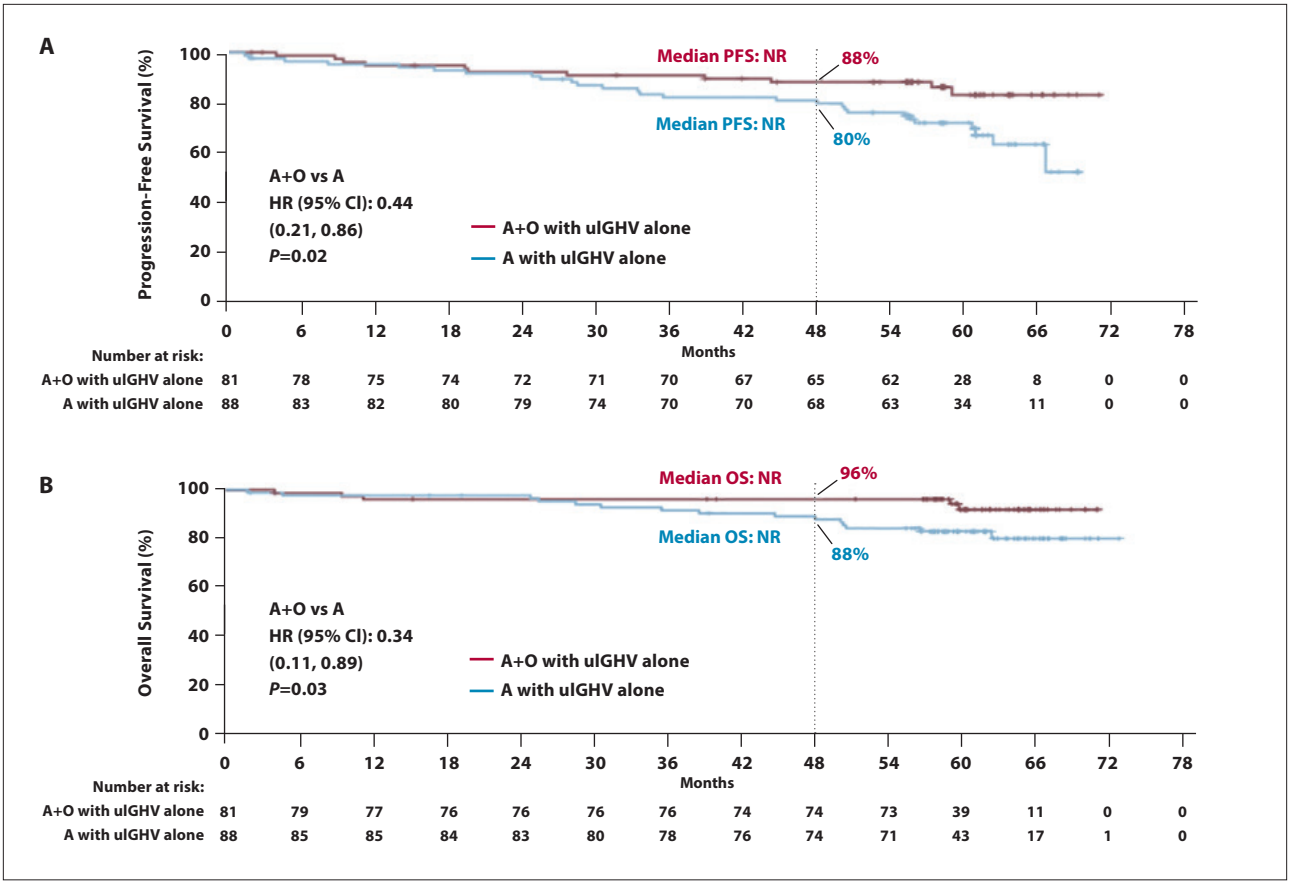


Figure 4. PFS (A) and OS (B) outcomes with acalabrutinib plus obinutuzumab vs acalabrutinib monotherapy among patients with CLL and unmutated *IGHV*. A, acalabrutinib monotherapy; A+O, acalabrutinib plus obinutuzumab; CLL, chronic lymphocytic leukemia; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; uIGHV, unmutated *IGHV*. Adapted from Davids MS, et al. ASH abstract 1815. *Blood*. 2022;140(suppl 1).

2. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia*. 2022;36(4):1171-1175.
3. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: five-year follow-up of ELEVATE-TN. *J Clin Oncol*. 2022;40(suppl 16):7539.
4. Woyach JA, Blachly JS, Rogers KA, et al. Acalabrutinib plus obinutuzumab in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia. *Cancer Discov*. 2020;10(3):394-405.
5. Davids MS, Sharman JP, Eyre TA, et al. Contribution of obinutuzumab to acalabrutinib therapy in patients with treatment-naive chronic lymphocytic leukemia: analysis of survival outcomes by genomic features [ASH abstract 1815]. *Blood*. 2022;140(Suppl 1).

Zanubrutinib Demonstrates Superior Progression-Free Survival (PFS) Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL): Results from Final Analysis of the ALPINE Randomized Phase 3 Study

The second generation BTK inhibitor zanubrutinib was designed to have greater BTK specificity than ibrutinib. As a result, zanubrutinib is hypothesized to have an improved toxicity profile compared with the first-generation agent ibrutinib. In previously untreated patients with CLL without del(17p), treatment with zanubrutinib resulted in superior PFS compared with bendamustine plus rituximab in the phase 3 SEQUOIA study.[1] In a late-breaking abstract presented at ASH 2022, final results from the phase 3 ALPINE study were presented and simultaneously published.[2,3] ALPINE was a head-to-head study comparing zanubrutinib with ibrutinib in patients with relapsed/refractory CLL/SLL.

The ALPINE study randomized

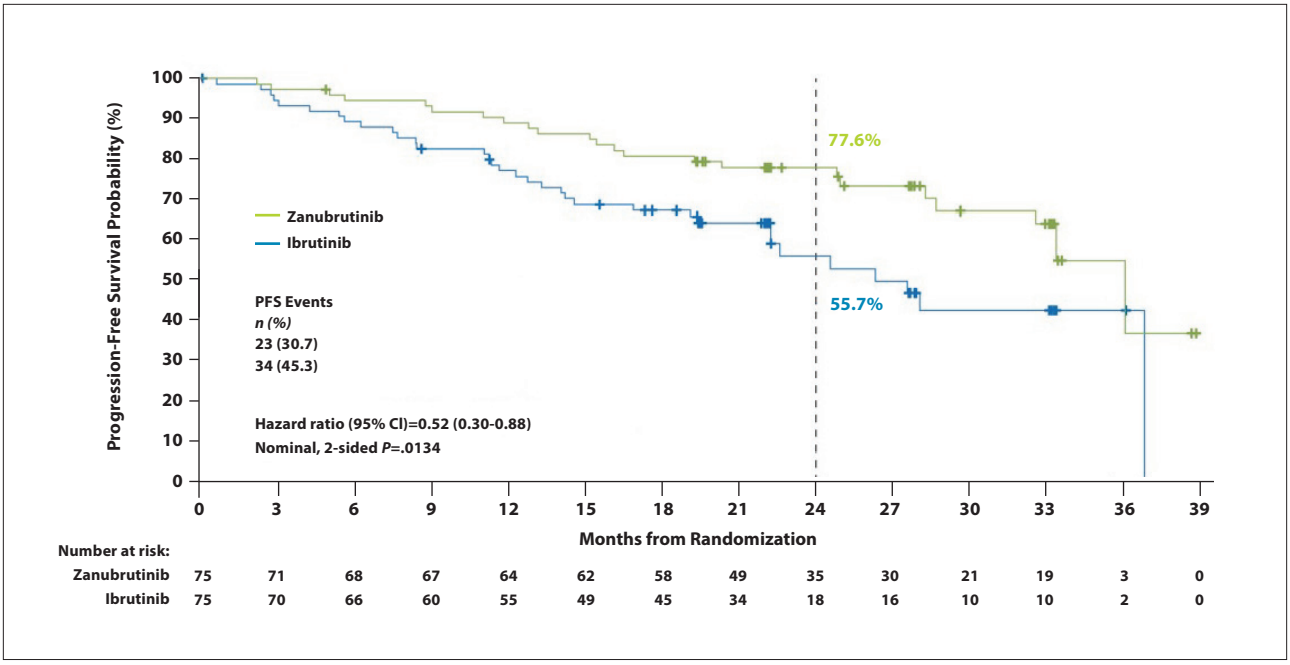


Figure 5. PFS with zanubrutinib vs ibrutinib among patients with relapsed/refractory CLL with del(17p)/*TP53* mutation in the ALPINE study. CLL, chronic lymphocytic leukemia; PFS, progression-free survival. Adapted from Brown JR, et al. ASH abstract LBA-6. *Blood*. 2022;140(suppl 1).

652 patients with relapsed/refractory CLL to treatment with zanubrutinib or ibrutinib. Patients were eligible for enrollment if they had measurable disease and had received at least 1 prior therapy (no prior BTK inhibitor therapy was allowed). The primary endpoint, ORR, was previously reported to have achieved statistical significance (78.3% with zanubrutinib vs 62.5% with ibrutinib; superiority 2-sided *P*=.0006).[4]

At the final analysis, at a median follow-up of 29.6 months, the median PFS was not reached with zanubrutinib vs 34.2 months with ibrutinib (HR, 0.65; 95% CI, 0.49-0.86; *P*=.002). PFS favored zanubrutinib across several patient subgroups, including in patients with del(17p)/*TP53* mutation (Figure 5). Fewer deaths were reported with zanubrutinib than with ibrutinib, and the median OS was not reached in either arm (HR, 0.76; 95% CI, 0.51-1.11).

Differences were also observed in the tolerability profiles of zanubrutinib and ibrutinib. The rate of grade 3 or higher adverse events was slightly higher with ibrutinib (67.3% with zanubrutinib vs 70.4% with ibrutinib). The incidence of any-grade atrial fibrillation and flutter, a key secondary endpoint, was 5.2% with zanubrutinib compared with 13.3% with ibrutinib (nominal 2-sided *P*=.0004). The incidence of grade 3 or greater atrial fibrillation and flutter events was also lower with zanubrutinib vs ibrutinib (2.5% vs 4.0%, respectively). Any-grade cardiac disorders were more common in ibrutinib-treated patients than in zanubrutinib-treated patients (21.3% with zanubrutinib vs 29.6% with ibrutinib). The incidence of any-grade and grade 3 or greater neutropenia was higher with zanubrutinib than with ibrutinib (any grade, 29.3% vs 24.4%; grade ≥3, 16.0% vs 13.9%, respectively). However, the rate of infections was not higher with zanubrutinib. Hypertension was reported in 23.5% of patients in the zanubrutinib arm and 22.8% of patients in the ibrutinib arm. Grade 3 hypertension was reported in 15.1% and 13.6% of the treatment arms, respectively. The incidence of hemorrhagic events, including major hemorrhagic events, were similar in both arms.

The study investigators concluded by noting that ALPINE was the first study to demonstrate both PFS and ORR superiority in a head-to-head comparison of BTK inhibitors in patients with relapsed/refractory CLL.

References

1. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2022;23(8):1031-1043.

2. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): results from final analysis of ALPINE randomized phase 3 study [ASH abstract LBA-6]. *Blood*. 2022;140(Suppl 1).

3. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2022 Dec 13. doi: 10.1056/NEJMoa2211582. Epub ahead of print. PMID: 36511784.

4. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: interim analysis of a randomized phase III trial. *J Clin Oncol*. 2022 Nov 17:JCO2200510. doi: 10.1200/JCO.22.00510. Epub ahead of print. PMID: 36395435.

MRD4 Eradication at 6 Months and Early Clearance of MRD with Combination of Ibrutinib Plus Venetoclax Results in Sustained Clinical and MRD Responses: Exploratory Analysis of the Blood Cancer UK TAP CLARITY Study

The CLARITY study evaluated the combination of ibrutinib and venetoclax in patients with relapsed/refractory CLL, with the intention of stopping treatment, depending on MRD response.[1] A 5-year follow-up of the CLARITY study was presented at ASH 2022, including an updated exploratory analysis of MRD eradication at 6 months and early clearance of MRD.[2]

A total of 54 patients were enrolled (50 patients were treated with the combination regimen). The treatment regimen began with a 2-month ibrutinib run-in followed by venetoclax introduction. The primary endpoint, undetectable MRD in the bone marrow, was assessed at 12 months of treatment with the combination therapy. The overall duration of therapy was determined by MRD analysis.

The primary endpoint, undetectable MRD in the bone marrow, was achieved by 40% of patients. The MRD negativity rate in the bone marrow was 45% among the 20 patients previously treated with FCR or bendamustine plus rituximab (BR) chemoimmunotherapy, and was 56% among the 9 patients who received prior idelalisib. In the peripheral blood, 58% of patients achieved an undetectable MRD (70% of patients previously treated with FCR or BR chemoimmunotherapy and 67% of patients previously treated with idelalisib).

The CR/CRi rate at month 38 was 78%, and the ORR was 92%. Most patients retained the response at the latest data cutoff. Neither median PFS nor median OS was reached by 60 months of follow-up. The estimated 5-year PFS was 78%; the estimated 5-year OS was 91%. No significant difference was observed in PFS or OS outcomes between *IGHV*-mutated and -unmutated patients, suggesting that both groups may benefit from the com-

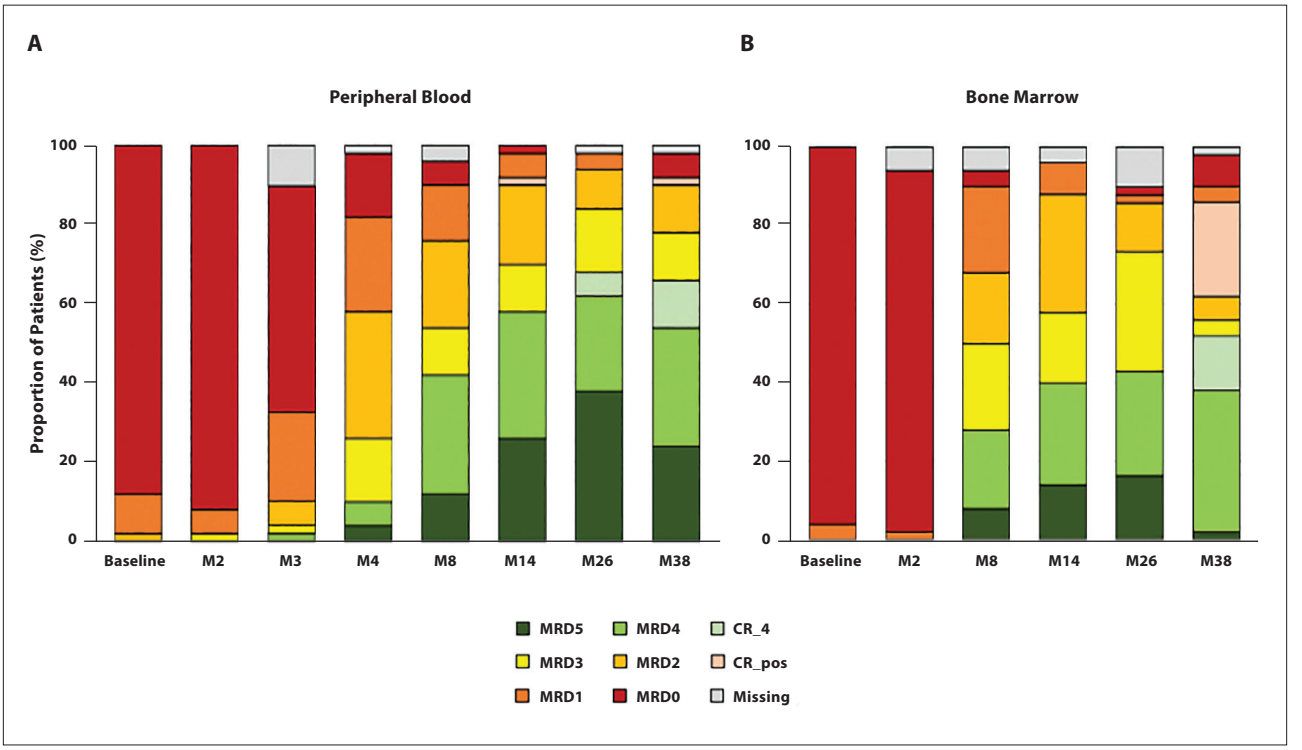


Figure 6. MRD responses in the peripheral blood (A) and bone marrow (B) in patients with relapsed/refractory CLL treated with ibrutinib plus venetoclax in the CLARITY study. MRD4 includes imputed MRD4 (previous BM <0.01% and current PB <0.001%); CR_4: previous BM MRD4/5 and remains in clinical remission with PB MRD4/5 where tested; CR_pos: remains in clinical remission with MRD >0.01% or not known; MRD0 includes MRD status unknown but clinical PR. BM, bone marrow; CLL, chronic lymphocytic leukemia; M, month; MRD, minimal residual disease; PB, peripheral blood. Adapted from Munir T, et al. ASH abstract 91. *Blood.* 2022;140(suppl 1).

bination of ibrutinib plus venetoclax.

MRD rates at various time points of the trial in both peripheral blood and bone marrow are shown in Figure 6. The sensitivity of combination was assessed according to leukocyte depletion in the peripheral blood at month 4 (after 2 months of combination treatment). A greater than 2-log leukocyte depletion in the first 2 months of treatment with the ibrutinib and venetoclax combination was associated with an improved MRD and clinical responses at later time points. This suggests that the initial rate of disease depletion is highly predictive of longer-term response to ibrutinib plus venetoclax.

References

1. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: the CLARITY study. *J Clin Oncol*. 2019;37(30):2722-2729.
2. Munir T, Cherrill L-R, Webster N, et al. MRD4 eradication at 6 months and early clearance of MRD with combination of ibrutinib plus venetoclax results in sustained clinical and MRD responses: exploratory analysis of the Blood Cancer UK TAP CLARITY study [ASH abstract 91]. *Blood*. 2022;140(Suppl 1).

Phase 1/2 Study of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Results with >4 Years of Follow-up

A final analysis of the phase 1/2 ACE-CL-001 study of acalabrutinib monotherapy in patients with relapsed/refractory CLL/SLL was reported at ASH 2022.[1] Earlier interim analyses have previously been reported.[2,3]

At a median follow-up of 52.6 months, 31% of the 134 patients initially enrolled remained on treatment. The ORR among patients in this study was 90%; of these, 4% were CRs. The median duration of response was 60.1 months, and the 66-month duration of response rate was 45%. The 72-month PFS rate was 45% in the overall population. The PFS rate was impacted by CLL genetics (Figure 7). For example, patients with unmutated *IGHV* had a 72-month PFS rate of 37%. For patients with a complex karyotype, the 72-month PFS rate was 20%. Among patients with del(17p), the 72-month PFS rate was 5%. At this long-term follow-up, no new safety signals were reported with acalabrutinib. The toxicity profile at 72 months was consistent with those reported at the earlier interim analyses.

References

1. Furman RR, Wierda WG, Schuh A, et al. Phase 1/2 study of acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: final results with >4 years of follow-up. [ASH abstract 4434]. *Blood*. 2022;140(Suppl 1).
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. 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.

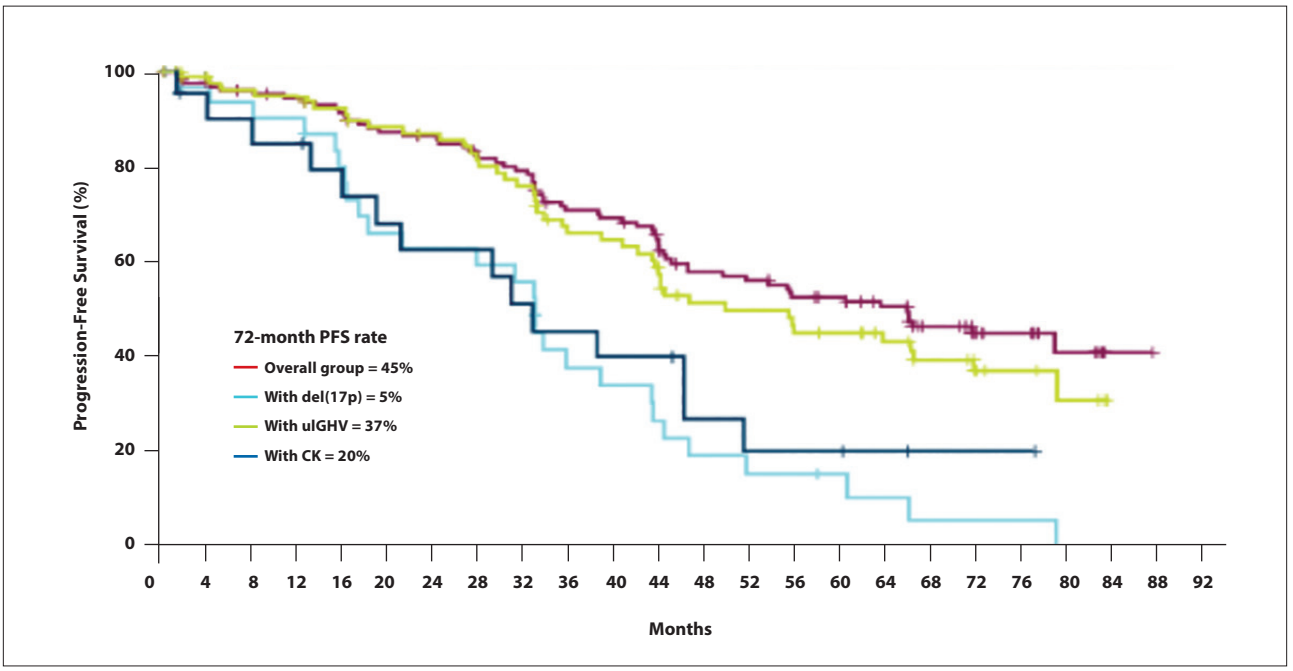


Figure 7. PFS outcomes at 72 months in a long-term follow-up of a phase 1/2 study of acalabrutinib in relapsed/refractory CLL. CK, complex karyotype; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; uIGHV, unmutated *IGHV*. Adapted from Furman RR, et al. ASH abstract 4434. *Blood*. 2022;140(suppl 1).

Efficacy of Pirtobrutinib in Relapsed/Refractory CLL and Richter Transformation: Additional Results From the Phase 1/2 BRUIN Study

Two studies presented at ASH 2022 examined pirtobrutinib, a novel, investigational, highly selective, noncovalent (reversible) BTK inhibitor. Pirtobrutinib has been shown to inhibit both wild-type and the BTK inhibitor-resistant C481-mutant version of BTK with equally high potency.[1] Both studies were analyses of the phase 1/2 BRUIN study, which evaluated pirtobrutinib in patients with relapsed or refractory B-cell malignancies, including CLL/SLL.[2]

The first study presented data from additional patients and an extended follow-up of the BRUIN study.[3] After more than 2 years of additional data, these updated results continued to demonstrate the efficacy of pirtobrutinib in patients with CLL/SLL who were previously treated with BTK inhibitors. The ORR was 82.2% among 247 patients; in 100 patients who had prior treatment with both a BTK inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor, the ORR was 79.0%. PFS was not significantly impacted by BTK C481 mutation status, age, *TP53* mutation and/or del(17p) status, or additional prior lines of therapy. Discontinuations owing to treatment-related adverse events were reported in 2.6% of patients.

The second study focused on the efficacy of pirtobrutinib in the cohort of 57 heavily pretreated patients with Richter transformation in the BRUIN study.[4] Historically, these patients have an extremely poor prognosis. The ORR among 50 evaluable patients was 54%, including 5 CRs and 22 PRs. After a median follow-up of 5.5 months, the median duration of response was 8.6 months (95% CI, 1.9 to not estimable). At a median follow-up of 9.7 months, the median OS was 13.1 months (95% CI, 7.1 to not estimable).

References

1. Wang E, Mi X, Thompson MC, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. *N Engl J Med*. 2022;386(8):735-743.
2. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901.
3. Mato AR, Woyach JA, Brown JR, et al. Efficacy of pirtobrutinib in covalent BTK-inhibitor pre-treated relapsed/refractory CLL/SLL: additional patients and extended follow-up from the phase 1/2 BRUIN study [ASH abstract 961]. *Blood*. 2022;140(Suppl 1).
4. Wierda WG, Lewis DJ, Ghia P, et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in richter transformation: results from the phase 1/2 BRUIN study [ASH abstract 347]. *Blood*. 2022;140(Suppl 1).

Initial Results from a Phase 1/2 Dose Escalation and Expansion Study Evaluating MS-553, a Novel and Selective PKCβ Inhibitor, in Patients with CLL/SLL

The B-cell receptor (BCR) signaling complex signals via a pathway composed sequentially of BTK, phospholipase C γ 2 (PLCγ2), and protein kinase C β (PKCβ).[1] Treatment with a BTK inhibitor can lead to the development of resistance mutations in BTK and PLCγ2.[2,3] As a result, downstream signaling can persist even in the presence of a BTK inhibitor. Because these mutations are in proteins that lie upstream of PKCβ, inhibition of this protein has the potential to overcome these resistance mutations.

MS-553 is a novel, investigational, selective PKCβ inhibitor. After preclinical studies demonstrated that MS-553 could reduce activation of primary CLL cells with both wild-type and C481-mutated BTK, a phase 1/2 dose escalation and expansion study was developed.[4,5] The initial results from this study were reported at ASH 2022.[6]

Key populations of patients enrolled in this study include those with relapsed/refractory disease; patients with relapsed/refractory disease and BTK or PLCγ2 mutations; previously untreated patients; and previously untreated patients with *TP53*-mutated CLL. A total of 43 patients were included in the initial analysis.

At this interim analysis, the ORR in patients with CLL was 48%. Further analysis also showed activity with MS-553 in combination with either acalabrutinib or venetoclax plus an anti-CD20 antibody, though the patient numbers were very small in the frontline setting. MS-553 was primarily associated with gastrointestinal-related toxicities, including nausea (60%), diarrhea (44%), decreased appetite (23%), vomiting (21%), abdominal pain (19%), and dysgeusia (12%). In contrast, side effects normally associated with BTK inhibitors (arthralgia, hemorrhage, atrial fibrillation, and others) were uncommon. A recommended phase 2 dosage was identified as 250 mg twice daily.

References

1. Gu D, Tang H, Wu J, Li J, Miao Y. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. *J Hematol Oncol*. 2021;14(1):40.
2. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294.
3. Wang E, Mi X, Thompson MC, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. *N Engl J Med*. 2022;386(8):735-743.
4. Muhowski EM, Lehman AM, S, MA, et al. The protein kinase C inhibitor MS-553 for the treatment of chronic lymphocytic leukemia. *Blood*. 2019;134 (Suppl 1):2077.
5. Clinicaltrials.gov. A Study of the selective PKC-β inhibitor MS- 553. Last updated November 21, 2022. Accessed January 17, 2023. https://clinicaltrials.gov/ct2/show/NCT03492125
6. Blachly JS, Stephens DM, Ye JC, et al. Initial results from a phase 1/2 dose escalation and expansion study evaluating MS-553, a novel and selective PKCβ inhibitor, in patients with CLL/SLL [ASH abstract 963]. *Blood*. 2022;140(Suppl 1).

Highlights in Chronic Lymphocytic Leukemia from the 2022 ASH Annual Meeting and Exposition: Commentary

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The 64th American Society of Hematology (ASH) Annual Meeting and Exposition took place in early December 2022 in New Orleans, Louisiana. It was good to see many colleagues at this in-person and virtual meeting, and a number of impactful studies were presented in CLL.

One of the main highlights in CLL was a presentation of the final results of the ALPINE study, which was a randomized phase 3 trial of zanubrutinib versus ibrutinib in patients with relapsed/refractory (R/R) CLL/SLL.[1] These results were simultaneously published.[2] The study enrollment was open to all patients with R/R CLL/SLL, including those with either high-risk genetic features or standard risk features. The investigators reported that PFS in patients treated with zanubrutinib was significantly improved compared with patients who received ibrutinib. The 2-year PFS was 79.5% in the zanubrutinib arm, and 67.3% in the ibrutinib arm. Importantly, 2-year PFS was also better with zanubrutinib in those patients with high-risk disease (i.e, *TP53* aberration): 77.6% vs 55.7% with ibrutinib. The safety data from this trial were previously described and demonstrated that zanubrutinib was associated with fewer cardiac events, particularly atrial fibrillation, as well as other adverse events.[4] The results were particularly important as they contributed to the recent US Food and Drug Administration (FDA) approval of zanubrutinib in patients with CLL.[3] This new indication allows use of zanubrutinib in both frontline and relapsed/refractory settings.

The final results from the ALPINE trial clearly indicate that zanubrutinib is superior to ibrutinib, both in terms of efficacy and safety, in R/R CLL/SLL. The fact that zanubrutinib also demonstrates improved efficacy in a high-risk patient population is particularly encouraging, further suggesting that this drug acts differently than ibrutinib.

One interesting feature from this study was that the rate of hypertension was similar between zanubrutinib (21.9%) and ibrutinib (19.8%) arm. This was somewhat in contrast to previous reports with zanubrutinib, for example in patients with Waldenström macroglobulinemia in the ASPEN study, where the rate of hypertension was higher with ibrutinib (16% versus 11% with zanubrutinib).[5] It is not yet clear if this difference in incidences is due to the study population or some other feature, but nevertheless it remains an important observation and patients with CLL who are treated with zanubrutinib should be monitored for hypertension.

Another point from ALPINE was that there was a fairly high discontinuation rate for both zanubrutinib (27.2%) and ibrutinib (41.5%). These discontinuation rates were a bit higher than we typically expect based on clinical trials of these agents in the past. However, it is notable that the ALPINE study enrolled patients in many countries, and also was conducted in recent years where patients may now have better access to novel agents and clinical trials. Thus, this study may in fact represent the current real world situation in terms of how frequently BTK inhibitors get discontinued for adverse events.

It may be that ibrutinib underperformed in terms of PFS in this study. For example, patients in the RESONATE study who had received 1 prior line of therapy—similar to the ALPINE study—had a higher PFS at 2 years than in this study.[6] Again, it is important to consider that the RESONATE study was conducted several years ago, and the treatment landscape for CLL has evolved since then.

A final note is that some publications now suggest that zanubrutinib may be associated with a distinct BTK mutational profile compared to ibrutinib when resistance occurs.[7] This may suggest a somewhat different biological effect of zanubrutinib compared with ibrutinib.

Several studies were presented which evaluated the combination of ibrutinib and venetoclax in patients with CLL. The GLOW study randomized patients with previously untreated CLL who did not have a *TP53* abnormality to either a combination of ibrutinib and venetoclax or chlorambucil and obinutuzumab.[8] This study led to approval of the ibrutinib plus venetoclax combination regimen in Europe; this regimen is not approved in the United States. The GLOW study revealed superior PFS for this combination over the control arm. The recently presented results also included

some granular data. We know, for example, that the combination of venetoclax plus obinutuzumab (the CLL14 regimen) demonstrates high efficacy in all patients with previously untreated CLL.[9] However, patients with unmutated *IGHV* demonstrate an inferior PFS with the combination of venetoclax plus obinutuzumab. We now begin to see a similar result in the GLOW study. After a median follow-up of 46 months, the curves begin to separate for PFS for patients with mutated vs unmutated *IGHV*. For patients with unmutated *IGHV* treated with the ibrutinib plus venetoclax combination, the PFS curve has dropped by about 20 percentage points at the 3-year follow-up mark, compared with mutated *IGHV*. This suggests what we have already suspected - this regimen will not be curative, and may not result in long-term remissions in patients with unmutated *IGHV*. Additionally, it remains to be seen if patients with previously untreated CLL will benefit from this regimen to the same degree as venetoclax plus obinutuzumab - CLL17 aims to answer that exact question.

An important feature of the ibrutinib-venetoclax combination is that it is an all-oral regimen and does not require intravenous administrations of an anti-CD20 antibody. However, a drawback of this all-oral regimen is that even though the GLOW regimen has an ibrutinib lead-in that can partially mitigate the risk for tumor lysis syndrome (TLS), it does not fully circumvent the need for TLS monitoring, and patients still need to come to the clinic for blood draws .

Another ibrutinib-based combination study presented was CAPTIVATE, which focused on the MRD cohort in this study.[10] After receiving an ibrutinib plus venetoclax combination, patients with confirmed undetectable MRD were randomized to continued treatment with either ibrutinib or placebo. The 4-year PFS rate was very high in both the ibrutinib and placebo arms (95% and 88%, respectively), suggesting that those patients who reach undetectable MRD with this combination are able to maintain the undetectable MRD state for several years, even after treatment stops. Interestingly, contrary to GLOW, patients with mutated and unmutated *IGHV* in the CAPTIVATE study showed statistically similar rates of PFS. However, the follow-up on the study may still be too short to see a difference here.

Both the GLOW and CAPTIVATE studies showed high efficacy with the oral combination regimen of ibrutinib and venetoclax. Whether this combination targeting dual pathways simultaneously is better than sequential therapy targeting BTK and BCL-2 separately remains to be seen.

An important caveat from these studies is that both use ibrutinib, a drug that was demonstrated to be less efficacious and associated with greater toxicities than zanubrutinib in the ALPINE study described above, and that also had inferior toxicity profile (albeit similar efficacy) to acalabrutinib in patients with high risk R/R CLL in the ELEVATE-R/R study.[1,2,11] This prompts the question of whether ibrutinib is the right partner in this oral combination. Studies investigating zanubrutinib and acalabrutinib in combination with venetoclax are ongoing.

Updated data from triplet regimens were also presented at ASH 2022. Data from a phase 2 study of acalabrutinib plus venetoclax and obinutuzumab in patients with previously treated CLL enriched for high-risk disease were presented.[12] These data demonstrated promising safety and efficacy with this triplet combination, but a longer follow-up is required.

The CLL2-GIVe trial, examining the triplet regimen of ibrutinib plus venetoclax and obinutuzumab in patients with previously untreated del(17p) or *TP53*-mutated CLL, were also presented.[13] This study demonstrated impressive PFS and OS (3-year PFS 79.9%; 3-year OS 92.6%) and high responses rates, but

ABSTRACT SUMMARY Initiating First-Line (1L) Ibrutinib (Ibr) in Patients (pts) with Chronic Lymphocytic Leukemia (CLL) Improves Overall Survival (OS) Outcomes to Rates Approximating an Age-Matched Population of ≥65 Years

A pooled analysis was conducted of patients with previously untreated CLL who received ibrutinib was conducted. This pooled analysis showed that frontline treatment with ibrutinib led to an improvement in OS as compared to chemotherapy or chemoimmunotherapy regimens (5-year OS rate 88% vs 75%; HR 0.46; 95% CI, 0.33-0.66; P <.0001). This benefit with ibrutinib was observed regardless of age and fitness, causing the investigators to hypothesize that some patients may completely avoid chemotherapy or chemoimmunotherapy. Further, dose reductions were shown to be an effective strategy to manage adverse events in most patients. Finally, the pooled group of patients treated with ibrutinib in the frontline were compared to the age-matched general population, showing a similar 8-year OS rate (78% vs 77%; HR 0.97; 95% CI, 0.63-1.51; P = .90).

Reference

Ghia P, Owen C, Barrientos JC, et al. Initiating first-line (1L) ibrutinib (Ibr) in patients (pts) with chronic lymphocytic leukemia (CLL) improves overall survival (OS) outcomes to rates approximating an age-matched population of ≥65 years [ASH abstract 1809]. *Blood*. 2022;140(Suppl 1).

the median follow-up of 38.4 months is relatively short.

Patients who progress on BTK inhibitors, and in particular those who are refractory to both BTK and BCL-2 inhibitors ("double-refractory") remain a high unmet medical need for whom there is no accepted standard of care. Pirtobrutinib, a noncovalent BTK inhibitor, may help address this gap. Pirtobrutinib has been studied in the phase 1/2 BRUIN study with additional updates presented at ASH. These updated results showed high response rates with pirtobrutinib in patients who received a prior BTK inhibitor and also in "double-refractory" patients.[14] It is also now known that resistance to this noncovalent BTK inhibitor can emerge via a set of novel resistance mutations.[15]

Efficacy of pirtobrutinib in patients with Richter transformation was also reported.[16] Among these patients who have no good treatment options, pirtobrutinib resulted in a response rate of 54%, with about 10% of patients achieving a CR. Importantly, several patients in this small study achieved long-term PFS and remained on the drug for longer than 6 months, which is remarkable for a single oral agent in this disease.

An innovative approach to circumvent BTK inhibitor resistance was highlighted in a first-in-human trial of NX-2127-001, a BTK protein degrader.[17] Instead of inhibiting the enzymatic activity of BTK, this agent utilizes the ubiquitin proteasome pathway to ubiquitinate BTK, leading to a decrease in BTK levels. This study included 23 patients with CLL, many of whom were refractory to both BTK and BCL-2 inhibitors. Eight patients had progressed on pirtobrutinib as well, and most patients had a BTK mutation present. NX-2127-001 was well tolerated, with side effects including fatigue, neutropenia, contusion, thrombocytopenia, hypertension, and atrial fibrillation which were overall characteristic of those seen with covalent BTK inhibitors. The very preliminary efficacy results show an ORR of 33% among the evaluable patients. Response assessments are ongoing. We certainly look forward to more data with this novel class of drug.

Finally, epcoritamab, a bispecific antibody, was evaluated in the EPCORE CLL-1 trial.[18] Even though only a small number of patients with Richter transformation were treated, 6 out of 10 achieved a response, with 5 patients showing a complete metabolic response. These data, coupled with other reports of various investigational bispecific antibodies, are very encouraging and suggest that bispecific antibodies may be a future option for these patients with a high unmet need.

Overall, several important and some practice-changing abstracts were presented at the ASH 2022 Annual Meeting. We look forward to further follow-up from the studies discussed here.

References

1. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): results from final analysis of ALPINE randomized phase 3 study [ASH abstract LBA-6]. *Blood*. 2022;140(Suppl 1).
2. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2022 Dec 13. doi: 10.1056/NEJMoa2211582. Epub ahead of print. PMID: 36511784.
3. Zanubrutinib [prescribing information]. San Mateo, CA; BeiGene USA, Inc. Revised January 2023.
4. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: interim analysis of a randomized phase III trial. *J Clin Oncol*. 2022 Nov 17:JCO2200510. doi: 10.1200/JCO.22.00510. Epub ahead of print. PMID: 36395435.
5. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050.
6. 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.
7. Blombery P, Thompson ER, Lew TE, et al. Enrichment of BTK Leu528Trp mutations in patients with CLL on zanubrutinib: potential for pirtobrutinib cross-resistance. *Blood Adv*. 2022;6(20):5589-5592.
8. Niemann CU, Munir T, Moreno C, et al. Residual disease kinetics among patients with high-risk factors treated with first-line fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O): the GLOW study [ASH abstract 93]. *Blood*. 2022;140(Suppl 1).
9. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.
10. Allan JN, Siddiqi T, Kipps TJ, et al. Treatment outcomes after undetectable MRD with first-line ibrutinib (Ibr) plus venetoclax (Ven): fixed duration treatment (placebo) versus continued Ibr with up to 5 years median follow-up in the CAPTIVATE study [ASH abstract 92]. *Blood*. 2022;140(Suppl 1).
11. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441-3452.
12. Ryan CE, Lampson BL, Tyekucheva S, et al. Updated results from a multicenter, phase 2 study of acalabrutinib, venetoclax, obinutuzumab (AVO) in a population of previously untreated patients with CLL enriched for high-risk disease [ASH abstract 344]. *Blood*. 2022;140(Suppl 1).
13. Huber H, Tausch E, Schneider C, et al. Final analysis of the prospective multicenter CLL2-GIVe trial of obinutuzumab (GA101, G), ibrutinib (I), and venetoclax (Ve) in untreated patients with CLL with 17p deletion/TP53 mutation [ASH abstract 343]. *Blood*. 2022;140(Suppl 1).
14. Mato AR, Woyach JA, Brown JR, et al. Efficacy of pirtobrutinib in covalent BTK-inhibitor pre-treated relapsed/refractory CLL/SLL: additional patients and extended follow-up from the phase 1/2 BRUIN study [ASH abstract 961]. *Blood*. 2022;140(Suppl 1).
15. Wang E, Mi X, Thompson MC, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. *N Engl J Med*. 2022;386(8):735-743.
16. Wierda WG, Lewis DJ, Ghia P, et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in Richter transformation: results from the phase 1/2 BRUIN study [ASH abstract 347]. *Blood*. 2022;140(Suppl 1).
17. Mato AR, Wierda WG, Ai WZ, et al. NX-2127-001, a first-in-human trial of NX-2127, a Bruton's tyrosine kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies [ASH abstract 965]. *Blood*. 2022;140(Suppl 1)
18. Kater AP, Ye JC, Sandoval-Sus J, et al. Subcutaneous epcoritamab in patients with Richter's syndrome: early results from phase 1b/2 trial (EPCORE CLL-1) [ASH abstract 348]. *Blood*. 2022;140(Suppl 1).