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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 63rd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 63rd ASH Meeting and Exposition • December 11-14, 2021 • Atlanta, Georgia

Special Reporting on:

- Three-Year Follow-Up of the ASCEND Trial: Acalabrutinib vs Rituximab Plus Idelalisib or Bendamustine in Relapsed/Refractory Chronic Lymphocytic Leukemia
- A Phase 2 Study Evaluating the Addition of Ublituximab and Umbralisib to Ibrutinib in Patients With Chronic Lymphocytic Leukemia: A Minimal Residual Disease–Driven, Time-Limited Approach
- New Acalabrutinib Formulation Enables Co-Administration With Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)
- Characterization of Bruton Tyrosine Kinase Inhibitor–Related Adverse Events in a Head-to-Head Trial of Acalabrutinib vs Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia
- A Quality-Adjusted Survival (Q-TWiST) Analysis to Assess Benefit-Risk of Acalabrutinib vs Idelalisib/Bendamustine Plus Rituximab or Ibrutinib Among Relapsed/Refractory Chronic Lymphocytic Leukemia Patients
- SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib vs Bendamustine + Rituximab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Pirtobrutinib, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results From the Phase 1/2 BRUIN Study
- Matching-Adjusted Indirect Treatment Comparison of Acalabrutinib Alone or in Combination With Obinutuzumab vs Ibrutinib or Venetoclax Plus Obinutuzumab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia
- A Randomized Phase 3 Study of Venetoclax-Based Time-Limited Combination Treatments vs Standard Chemoimmunotherapy in Frontline Chronic Lymphocytic Leukemia of Fit Patients: First Co–Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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CALQUENCE®
(acalabrutinib) 100 mg capsules

CALQUENCE CONFIDENCE

ELEVATE-RR: THE FIRST PHASE 3 HEAD-TO-HEAD TRIAL OF CALQUENCE VS IBRUTINIB IN R/R CLL[1]

Study Design[2]

A randomized, multicenter, open-label, Phase 3 trial of CALQUENCE vs ibrutinib in patients with relapsed/refractory CLL with the presence of 17p deletion and/or 11q deletion. Patients (N=533) were randomized 1:1 to receive either CALQUENCE 100 mg orally twice daily or ibrutinib 420 mg orally once daily until disease progression or unacceptable toxicity. Primary endpoint was PFS by IRC assessment (non-inferiority; tested after ≈250 events). Secondary endpoints were incidence of any-grade atrial fibrillation, incidence of Grade ≥3 infections, incidence of Richter's transformation, and OS.

SELECT EVENTS OF CLINICAL INTEREST[2]

	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

All 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.[2]

The most common AEs of any grade (≥20%) in patients receiving CALQUENCE were infections, bleeding, diarrhea, headache, cough, upper respiratory tract infection, neutropenia, pyrexia, anemia, and fatigue.[2]

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.[2]

*Defined as the preferred terms atrial fibrillation and atrial flutter.[2]
†Includes events with preferred terms: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation.[2]
‡Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any-severity grade).[2]
§Defined as the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.[2]
‖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%).[2]

ASCEND: THE FIRST STUDY OF A BTKi VS IdR OR BR IN R/R CLL[3]

Study Design[3,4]

A Phase 3, open-label, randomized, multicenter trial in patients with relapsed/refractory CLL. Patients (N=310) were randomized 1:1 to either receive CALQUENCE monotherapy 100 mg approximately every 12 hours until disease progression or unacceptable toxicity, or investigator's choice of IdR or BR. Primary endpoint at the interim analysis was IRC-assessed PFS. Primary endpoint in the final analysis was investigator-assessed PFS. Select secondary endpoints were ORR, OS, and safety.

EVENTS OF CLINICAL INTEREST[4]

	CALQUENCE (n=154)		IdR (n=118)		BR (n=35)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
CARDIOVASCULAR EVENTS						
Cardiac events	13	3	8	3	9	9
Atrial fibrillation	5	1	3	1	3	3
Ventricular tachyarrhythmias*	0	0	0	0	0	0
Bleeding	26	2	8	3	6	3
Major bleeding†	2	2	3	3	3	3
Hypertension	3	2	4	1	0	0
OTHER						
Hepatotoxicity‡	5	2	28	22	9	6
Infections	57	15	65	28	49	11

At interim analysis,[5] the most common AEs (≥20%) of any grade in patients receiving CALQUENCE were infection, neutropenia, anemia, thrombocytopenia, lymphocytopenia, and headache.[3]

The median duration of exposure to CALQUENCE was 15.7 months.[3]

*All Grade cardiac arrhythmias of unspecified origin were reported, including arrhythmia (0.7%), bradycardia (0.7%), and tachycardia (0.7%) for CALQUENCE.[3]
†Defined as any serious or grade ≥3 bleeding or central nervous system bleeding of any grade. In the acalabrutinib group, events were gastrointestinal hemorrhage (n=2) and immune thrombocytopenic purpura (n=1); for idelalisib plus rituximab, gastrointestinal hemorrhage, immune thrombocytopenic purpura, and hematuria (n=1 each); and for bendamustine plus rituximab, hemorrhagic anemia and tumor hemorrhage (both in 1 patient).[3]
‡Defined as a select group of hepatic events including hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions, liver-related investigations, abnormalities, and noninfectious hepatitis.[3]
§Median 16.1-month follow-up.[4]

AEs=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BR=bendamustine + rituximab; BTKi=Bruton tyrosine kinase inhibitor; CLL=chronic lymphocytic leukemia; IdR=idelalisib + rituximab; IRC=independent review committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory.

IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) capsules

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.

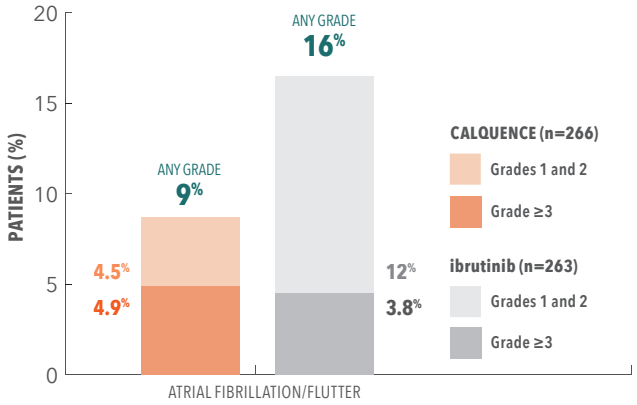
IN RELAPSED/REFRACTORY CLL

LOW RATES OF ATRIAL FIBRILLATION[2,4]

VIEW HEAD-TO-HEAD TRIAL RESULTS

ELEVATE-RR: CALQUENCE VS IBRUTINIB

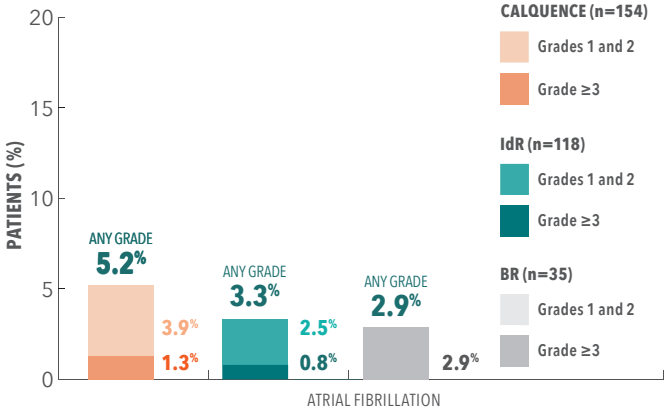
LOW RATES OF ATRIAL FIBRILLATION/FLUTTER ACROSS SEVERITY/GRADES[2]



ASCEND: CALQUENCE VS IdR OR BR

LOW RATES OF ATRIAL FIBRILLATION AT THE INTERIM ANALYSIS*[4]

*The interim analysis had a median follow-up of 16.1 months.



RATES OF NEW ONSET ATRIAL FIBRILLATION/FLUTTER (ANY GRADE) IN ELEVATE-RR IN PATIENTS WITHOUT HISTORY OF ATRIAL FIBRILLATION/FLUTTER[2]

6% (15/243) for CALQUENCE — **15%** (37/249) for ibrutinib

Among patients who experienced atrial fibrillation/flutter events, **0 patients discontinued treatment in the CALQUENCE arm** and 7 (17%) discontinued treatment in the ibrutinib arm[2]

IMPORTANT SAFETY INFORMATION (CONT'D)

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

ADVERSE REACTIONS
The 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 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), dosage 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 1.5 to 3 times the upper limit of normal occurred in 1.3% of patients who received CALQUENCE.

DRUG INTERACTIONS
Strong CYP3A Inhibitors: Avoid co-administration with a strong CYP3A inhibitor. If a strong CYP3A inhibitor will be used short-term, interrupt CALQUENCE.
Moderate CYP3A Inhibitors: When CALQUENCE is co-administered with a moderate CYP3A inhibitor, reduce CALQUENCE dose to 100 mg once daily.
Strong CYP3A Inducers: Avoid co-administration with a strong CYP3A inducer. If a strong CYP3A inducer cannot be avoided, increase the CALQUENCE dose to 200 mg approximately every 12 hours.
Gastric Acid Reducing Agents: If treatment with a gastric acid reducing agent is required, consider using an H2-receptor antagonist or an antacid. Take CALQUENCE 2 hours before taking an H2-receptor antagonist. Separate dosing with an antacid by at least 2 hours. Avoid co-administration with proton pump inhibitors. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

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 at least 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 at least 2 weeks after the final dose. Avoid administration of CALQUENCE in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment.

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

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

References:
1. Study of Acalabrutinib (ACP-196) Versus Ibrutinib in Previously Treated Subjects With High Risk CLL. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477696. Published June 23, 2015. Accessed October 29, 2021. **2.** 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*. Published online July 26, 2021:JCO.21.01210 and supplementary appendix.
3. CALQUENCE [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.
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.

AstraZeneca

CALQUENCE® (acalabrutinib) 100 mg capsules

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

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

CALQUENCE as Monotherapy

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

CALQUENCE in Combination with Obinutuzumab

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

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

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

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

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

Recommended Dosage for Drug Interactions

Dose Modifications for Use with CYP3A Inhibitors or Inducers

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

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

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

Concomitant Use with Gastric Acid Reducing Agents

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

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

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

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

Table 2: Recommended Dose Modifications for Adverse Reactions

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

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

Chronic Lymphocytic Leukemia

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*Per NCI CTCAE version 4.03
[a] Excludes electrolytes

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

ASCEND

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

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

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

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

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

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

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

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

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

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

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

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

Per NCI CTCAE version 5
[a] Excludes electrolytes

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy

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

Contraception

Females

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

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Three-Year Follow-Up of the ASCEND Trial: Acalabrutinib vs Rituximab Plus Idelalisib or Bendamustine in Relapsed/Refractory Chronic Lymphocytic Leukemia

Acalabrutinib is a second-generation inhibitor of Bruton tyrosine kinase (BTK) approved for the treatment of chronic lymphocytic leukemia (CLL).[1] The phase 3 ASCEND trial evaluated acalabrutinib vs the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab. Eligible patients were adults with a diagnosis of CLL (as defined by the International Workshop on CLL [iwCLL]) who had received at least 1 prior systemic therapy. The trial enrolled 310 patients. Stratification factors included presence of the 17p deletion (del[17p]), Eastern Cooperative Oncology Group (ECOG) performance status, and number of prior therapies. Patients were randomly assigned to receive acalabrutinib (100 mg, twice daily) vs idelalisib (150 mg, twice daily) plus rituximab or bendamustine (70 mg/m^2) plus rituximab. The primary endpoint was investigator-assessed progression-free survival (PFS). Patients with disease progression in the rituximab arm were allowed to cross over into the acalabrutinib arm.

The patients' median age was 67 years (range, 32-90 years). They had received a median of 2 prior therapies (range, 1-10 prior therapies). Bulky disease (≥5 cm) was noted in 48.7% of patients, and 41.6% had Rai stage III/IV disease. Cytogenetic abnormalities included unmutated immunoglobulin heavy chain (IGHV) in 78.4%, complex karyotype in 31.0%, del(11q) in 26.8%, and del(17p) in 15.8%. The median time on study was similar for all 3 treatment regimens (range, 34.2-36.0 months).[2] The median duration of exposure was 35.0 months with acalabrutinib, 11.5 months with idelalisib plus rituximab, and 5.6 months with bendamustine plus rituximab. Treatment was discontinued by 19% of patients in the bendamustine arm, 43% of patients in the acalabrutinib arm, and 85% of patients in the idelalisib arm.

The median PFS was not reached with acalabrutinib vs 16.8 months with pooled data from the 2 rituximab cohorts (hazard ratio [HR], 0.29; 95% CI, 0.21-0.41; *P*<.0001). The 3-year PFS was 63% vs 21%, respectively. Acalabrutinib also yielded superior PFS vs idelalisib plus rituximab (HR, 0.31; 95% CI, 0.22-0.43; *P*<.0001) or bendamustine plus rituximab (HR, 0.25; 95% CI, 0.16-0.40; *P*<.001; Figure 1). The median PFS was higher with acalabrutinib vs the investigator's choice of therapy among patients with del(17p) (HR, 0.13; 95% CI, 0.06-0.30; *P*<.0001) or without del(17p) (HR, 0.34; 95% CI, 0.24-0.48; *P*<.0001; Figure 2). Similar improvements in median PFS were reported for patients with unmutated *IGHV* (HR, 0.30; 95% CI, 0.21-0.42; *P*<.0001) or with mutated *IGHV* (HR, 0.32; 95% CI, 0.14-0.70; *P*<.0027). Treatment with acalabrutinib yielded a superior median PFS compared with the rituximab combinations in all prespecified

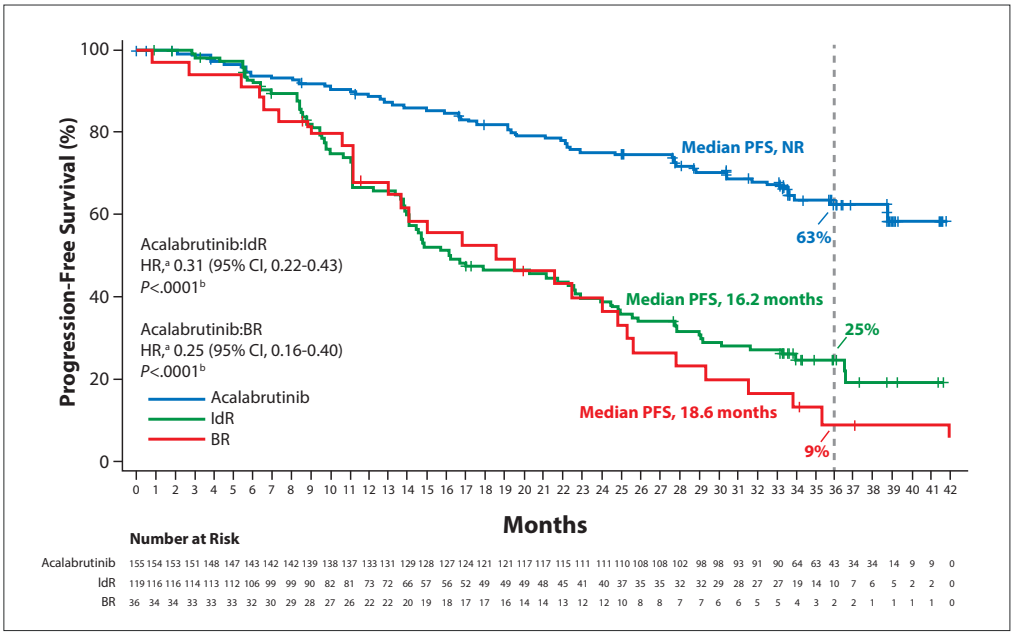

Figure 1. PFS in a 3-year follow-up analysis of the phase 3 ASCEND trial. [a]Hazard ratios were based on a stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in an interactive voice/web response system. [b]*P* value was based on a stratified log-rank test, stratified by the same factors. BR, bendamustine plus rituximab; HR, hazard ratio; IdR, idelalisib plus rituximab; NR, not reached; PFS, progression-free survival. Adapted from Jurczak W et al. ASH abstract 393. *Blood*. 2021;138(suppl 1).[2]

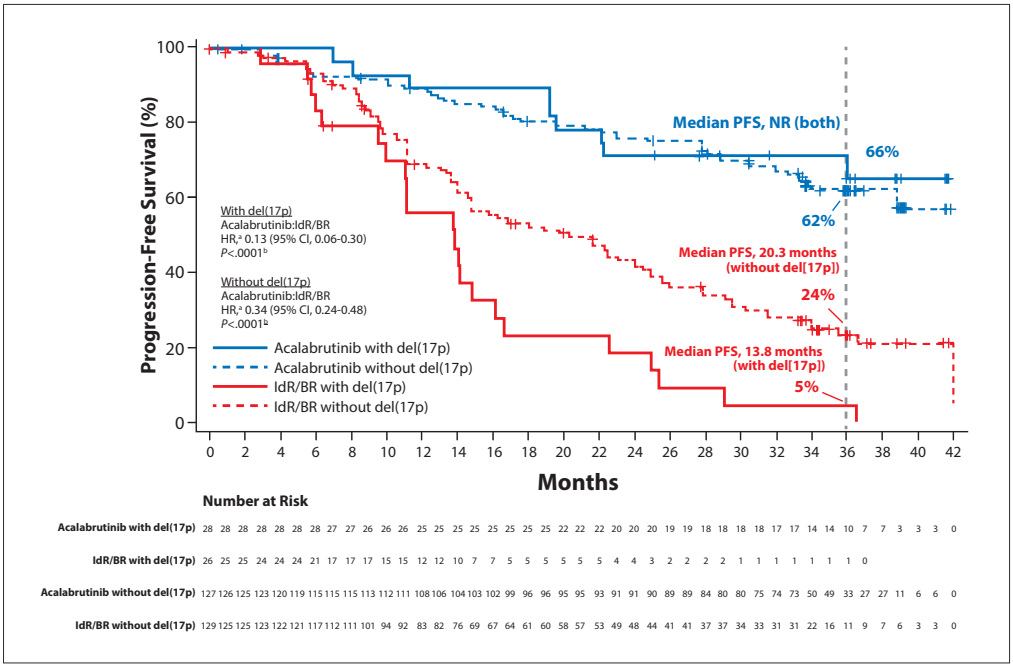

Figure 2. PFS in patients with or without deletion 17p in a 3-year follow-up analysis of the phase 3 ASCEND trial. [a]Hazard ratios were based on an unstratified Cox proportional hazards model. [b]*P* values were based on an unstratified log-rank test. BR, bendamustine plus rituximab; HR, hazard ratio; IdR, idelalisib plus rituximab; NR, not reached; PFS, progression-free survival. Adapted from Jurczak W et al. ASH abstract 393. *Blood*. 2021;138(suppl 1).[2]

subgroups, including those based on number of prior therapies, Rai stage at screening, bulky disease, and complex karyotype. The median overall survival (OS) was not reached in either arm. At 2 years, however, the Kaplan-Meier curves showed separation between patients treated with acalabrutinib vs the investigator's choice. The 3-year OS rates were 80% with acalabrutinib vs 73% with the rituximab-containing therapies (HR, 0.69; 95% CI, 0.43-1.10; *P*=.1184). The objective response rate was similar for acalabrutinib vs the investigator's choice of therapy (83% vs 85%, respectively; *P*=.62).

Adverse events (AEs) of grade 3 or higher were observed in 62% of patients in the acalabrutinib arm, 92% in the idelalisib plus rituximab arm, and 49% in the bendamustine plus rituximab arm. Grade 5 AEs were observed in 9%, 7%, and 6% of patients, respectively. AEs led to treatment discontinuation in 21%, 65%, and 17%. Serious AEs associated with acalabrutinib therapy included pneumonia (8%), pyrexia (2%), and diarrhea (1%).

References

1. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther*. 2017;363(2):240-252.
2. Jurczak W, Pluta A, Wach M, et al. Three-year follow-up of the ASCEND trial: acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia [ASH abstract 393]. *Blood*. 2021;138(suppl 1).

A Phase 2 Study Evaluating the Addition of Ublituximab and Umbralisib to Ibrutinib in Patients With Chronic Lymphocytic Leukemia: A Minimal Residual Disease–Driven, Time-Limited Approach

A phase 2 trial evaluated induction with ibrutinib monotherapy, followed by ublituximab plus umbralisib (U2), in patients with detectable minimal residual disease (MRD).[1] The multicenter, open-label trial enrolled patients who were receiving ongoing ibrutinib as any line of therapy for at least 6 months. Patients had detectable residual CLL in the peripheral blood according to flow cytometry, with a cutoff of 10^{-4}. For patients with detectable MRD, U2 was added to ibrutinib therapy. Patients were serially monitored for MRD starting on day 1 of cycle 3. Patients who remained MRD-free for 4 weeks underwent treatment-free observation. Patients with detectable MRD continued with combination therapy for up to 24 cycles. The primary endpoint was the rate of undetectable MRD.

Twenty-eight patients were evaluable for safety and 27 for efficacy. The patients were a median age of 64 years (range, 48-81 years). The median duration of ibrutinib monotherapy at study entry was 21 months (range, 7-67 months). Sixty-eight percent of patients were receiving ibrutinib monotherapy as their first-line therapy, and all of the patients had achieved a partial response (PR) as their best

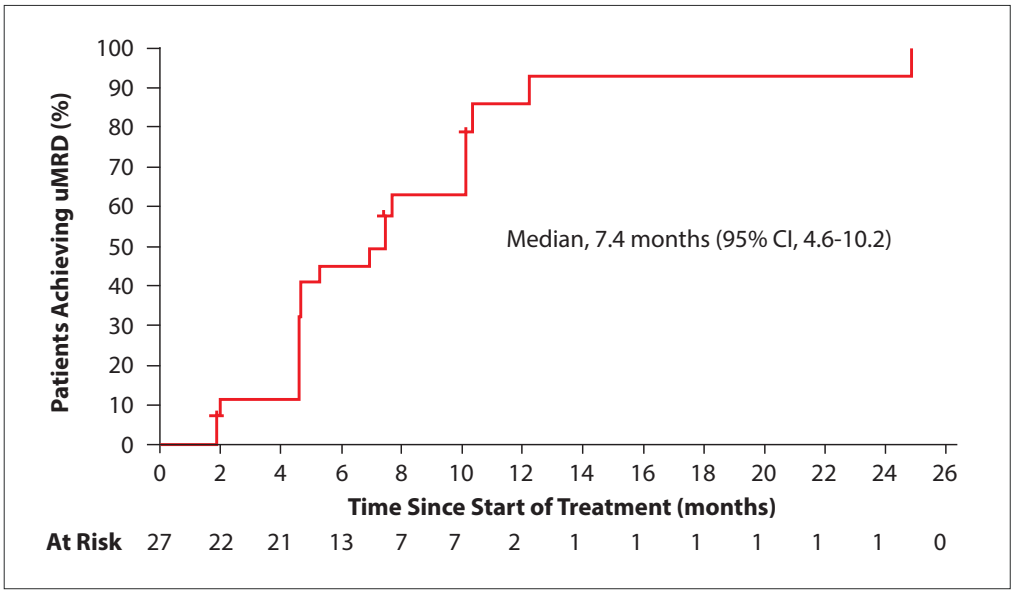

Figure 3. Rates of uMRD among patients with chronic lymphocytic leukemia treated with ublituximab and umbralisib plus ibrutinib in a phase 2 trial. MRD, undetectable minimal residual disease. Adapted from Roeker LE et al. ASH abstract 395. *Blood*. 2021;138(suppl 1).[1]

response during treatment with ibrutinib. Cytogenetic features included unmutated *IGHV* in 67%, del(11q) in 21%, and del(17p) in 7%. Two patients discontinued study therapy owing to AEs consisting of rash and/or arthralgia. Grade 3/4 treatment-emergent AEs included hypertension (7%), diarrhea (4%), elevated transaminases (4%), and COVID-19 (4%). One patient died of COVID-19 complications 103 days after discontinuing the U2 regimen and was not included in the efficacy evaluations.

Seventy-seven percent of patients achieved undetectable MRD. Nineteen percent of patients had detectable MRD and were continuing therapy, and 1 patient had completed 24 cycles of therapy and had detectable MRD. The median time to undetectable MRD was 7.4 months (95% CI, 4.6-10.2 months; Figure 3). At the time of the report, only 1 patient had developed progressive disease.

Reference

1. Roeker LE, Leslie L, Soumerai J, et al. A phase 2 study evaluating the addition of ublituximab and umbralisib to ibrutinib in patients with chronic lymphocytic leukemia: a minimal residual disease–driven, time-limited approach [ASH abstract 395]. *Blood*. 2021;138(suppl 1).

New Acalabrutinib Formulation Enables Co-Administration With Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

Acalabrutinib is approved for the treatment of CLL and mantle cell lymphoma.[1] The solubility of acalabrutinib decreases with increasing pH, and therefore concomitant use of proton pump inhibitors is not recommended.[2] Additionally, cancer patients who have difficulty swallowing capsules may require an alternative method of delivery. To address these issues, acalabrutinib was developed in a tablet form with an immediate-release film.[3] The film coating eases swallowing of the tablet, and the tablet's volume is reduced by 50% compared with the capsule formulation. The acalabrutinib maleate tablet is quickly and completely released in vitro at all physiologic pH levels.

Three open-label, single-dose, crossover phase 1 studies were conducted to assess the pharmacologic and clinical properties of the acalabrutinib maleate tablet or acalabrutinib suspension formulation as compared with the capsules. The investigators also evaluated the effects of a high-fat diet vs fasting on the properties of the tablet. These studies included 66 subjects to establish pharmacokinetic similarity between the acalabrutinib maleate tablet (100 mg) and the acalabrutinib capsule (100 mg); 14 patients who received the acalabrutinib maleate tablet (100 mg) plus rabeprazole; 16 patients who received the acalabrutinib maleate tablet (100 mg) while following a high-fat diet or in a fasting state; and 20 patients who received the acalabrutinib maleate (100 mg) suspension delivered by a nasogastric tube for the assessment of pharmacokinetics. Pharmacodynamics were evaluated by measuring the BTK target occupancy in peripheral blood mononuclear cells.

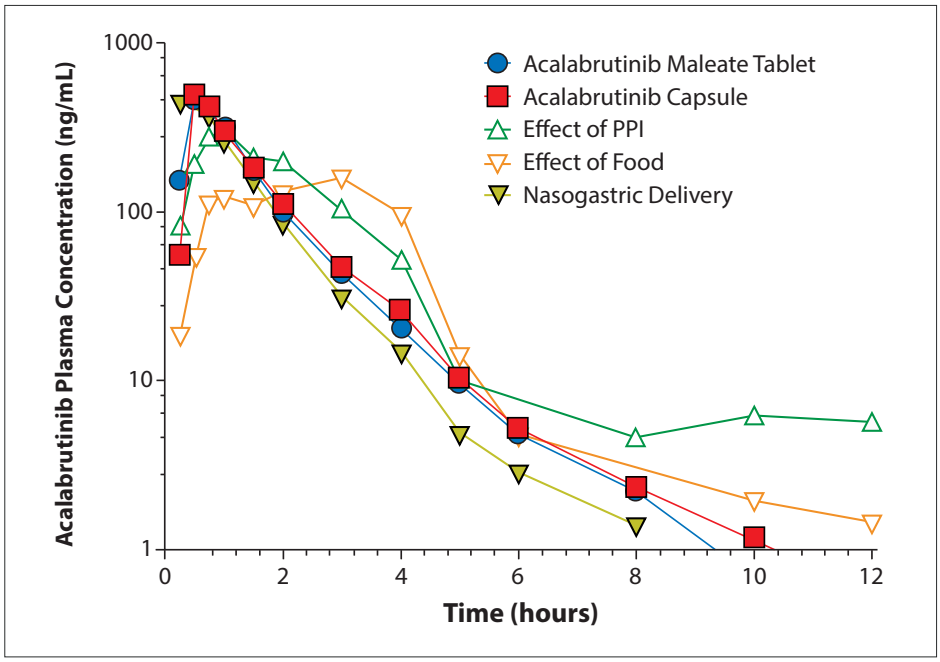

Figure 4. Plasma concentration of acalabrutinib administered in various formulations, with food, and with a PPI in phase 1 studies. PPI, proton pump inhibitor. Adapted from Sharma S et al. ASH abstract 4365. *Blood*. 2021;138(suppl 1).[3]

Systemic exposure of acalabrutinib and ACP-5862—its most prevalent pharmacologically active metabolite—were bioequivalent between acalabrutinib and the acalabrutinib maleate tablet, showing a difference in the geometric mean exposures of less than 5% (Figure 4). The addition of a proton pump inhibitor to the acalabrutinib maleate tablet did not confer any clinically relevant differences in exposure to acalabrutinib or ACP-5862. The BTK target occupancy was at least 95% across all treatment arms. A high-fat diet did not affect exposure to acalabrutinib or ACP-5862, with a BTK target occupancy of 95% or higher observed across all treatment arms. Exposure to acalabrutinib and ACP-5862 was equivalent, with a difference of no more than 10% across the acalabrutinib maleate suspension (100 mg), delivery via nasogastric tube, and the acalabrutinib capsules (100 mg). Exposure to acalabrutinib and its major active metabolite was also equivalent between the capsules and the nasogastric suspension among the patients who did or did not receive a proton pump inhibitor. The novel acalabrutinib tablet formulation was associated with a favorable safety profile. The majority of AEs were mild, with no serious cases reported.

References

1. Calquence [package insert]. Wilmington, DE; AstraZeneca, Inc; 2019.
2. Pepin XJH, Moir AJ, Mann JC, et al. Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part II. A mechanistic PBPK model for IR formulation comparison, proton pump inhibitor drug interactions, and administration with acidic juices. *Eur J Pharm Biopharm*. 2019;142:435-448.
3. Sharma S, Pepin X, Burri H, et al. New acalabrutinib formulation enables co-administration with proton pump inhibitors and dosing in patients unable to swallow capsules (ELEVATE-PLUS) [ASH abstract 4365]. *Blood*. 2021;138(suppl 1).

Characterization of Bruton Tyrosine Kinase Inhibitor–Related Adverse Events in a Head-to-Head Trial of Acalabrutinib vs Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

The ongoing phase 3 ELEVATE-RR trial is comparing acalabrutinib vs ibrutinib in previously treated patients with CLL.[1,2] The study enrolled 533 patients with centrally confirmed del(17p13.1) or del(11q22.3). Patients were randomly assigned to receive acalabrutinib (100 mg, twice daily) or ibrutinib (420 mg, daily) until disease progression or unacceptable toxicity. The patients were a median age of 66 years. Del(17p) was noted in 45% of patients and del(11q) was reported in 64%. After a median follow-up of 40.9 months, the median PFS in both arms was 38.4 months, thus demonstrating noninferiority of acalabrutinib compared with ibrutinib (HR, 1.00; 95% CI, 0.79-1.27). Safety results suggested a reduction in cardiovascular AEs in the acalabrutinib arm.

A post hoc analysis was conducted to provide a more detailed comparison

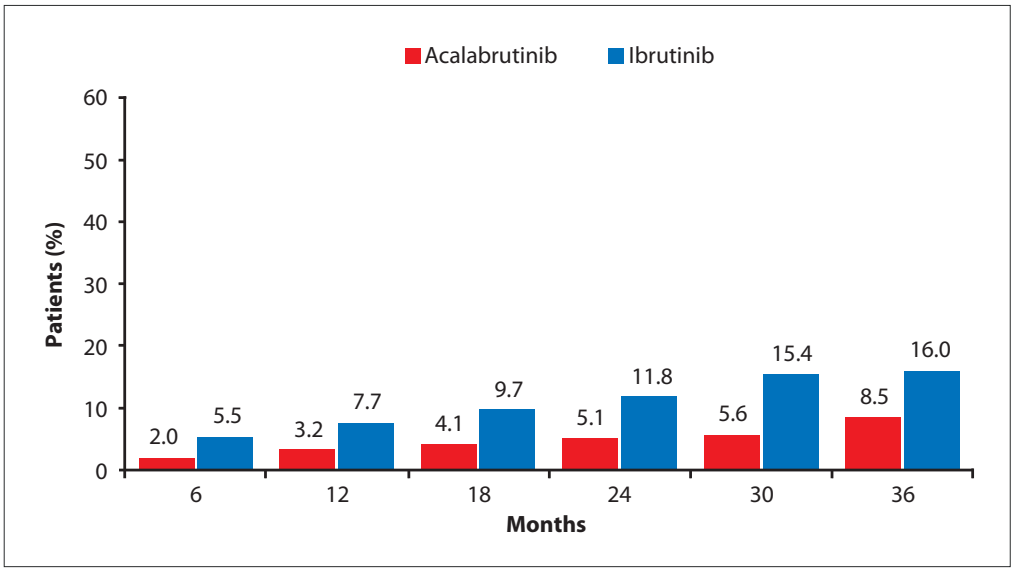

Figure 5. Cumulative incidence of any-grade atrial fibrillation/flutter among patients in the ELEVATE-RR trial, which compared acalabrutinib vs ibrutinib in patients with previously treated chronic lymphocytic leukemia. Adapted from Seymour JF et al. ASH abstract 3721. *Blood*. 2021;138(suppl 1).[2]

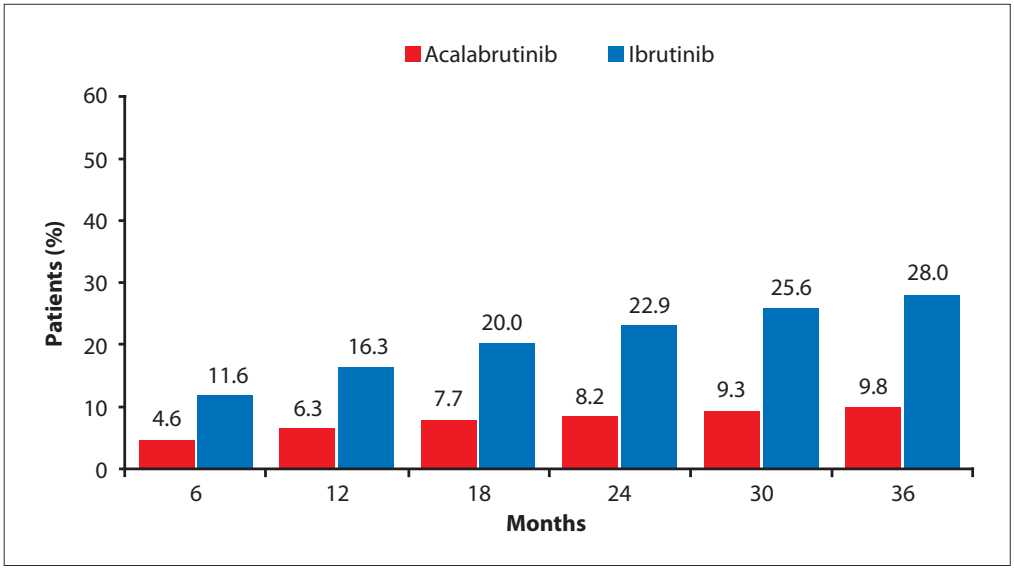

Figure 6. Cumulative incidence of any-grade hypertension in the ELEVATE-RR trial, which compared acalabrutinib vs ibrutinib in patients with previously treated chronic lymphocytic leukemia. Adapted from Seymour JF et al. ASH abstract 3721. *Blood*. 2021;138(suppl 1).[2]

of the rates of AEs with acalabrutinib vs ibrutinib.[2] The median treatment exposure was 38.3 months with acalabrutinib vs 35.5 months with ibrutinib. Ibrutinib was associated with an exposure-adjusted higher incidence rate of any-grade atrial fibrillation/flutter (2-fold; Figure 5), hypertension (2.8-fold; Figure 6), and bleeding (1.6-fold). The exposure-adjusted time with event was also greater with ibrutinib by 2.0-, 3.7-, and 1.8-fold, respectively. Ventricular arrhythmias occurred in 3 patients in the ibrutinib arm vs none in the acalabrutinib arm. Sudden cardiac death occurred in 1 additional patient in the ibrutinib arm vs none in the comparator arm. The exposure-adjusted incidence was higher with ibrutinib compared with acalabrutinib in terms of any-grade diarrhea (2.8 vs 1.9), arthralgia (1.3 vs 0.6), back pain (0.5 vs 0.3), muscle spasms (0.7 vs 0.2), and dyspepsia (0.5 vs 0.1). Acalabrutinib was associated with a higher exposure-adjusted incidence of cough (1.1 vs 1.3) and headache (1.1 vs 1.8).

Further characterization showed a prolonged median time to onset of atrial fibrillation/flutter of any grade with acalabrutinib (28.8 months [range, 0.4-52.0 months]) vs ibrutinib (16.0 months [range, 0.5-48.3 months]). The cumulative incidence of atrial fibrillation/flutter was lower with acalabrutinib compared with ibrutinib at all time points examined. The median time to hypertension was similar for acalabrutinib (8.1 months [range, 0.0-44.0 months]) and ibrutinib (7.0 months [range, 0.0-39.8 months]). However, the cumulative incidence of hypertension was lower with acalabrutinib for each time point examined. Based on Cox proportional hazard modeling,

acalabrutinib was favored over ibrutinib with rate reductions of 63% for new-onset atrial fibrillation/flutter and 77% for new-onset hypertension. The lower incidences of atrial fibrillation/flutter and hypertension reported with acalabrutinib were maintained in all subgroups. The median time to onset of bleeding was 1.2 months for both treatments. However, the cumulative incidence of any-grade bleeding events was lower with acalabrutinib compared with ibrutinib at every time point examined.

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A Quality-Adjusted Survival (Q-TWiST) Analysis to Assess Benefit-Risk of Acalabrutinib vs Idelalisib/Bendamustine Plus Rituximab or Ibrutinib Among Relapsed/Refractory Chronic Lymphocytic Leukemia Patients

The ELEVATE-RR trial and the ASCEND study investigated acalabrutinib among patients with previously treated CLL, with overall study populations of 533 and 310, respectively.[1,2] The comparator arm received treatment with ibrutinib monotherapy in the ELEVATE-RR study and rituximab plus idelalisib or bendamustine in the ASCEND study. A post hoc analysis was conducted to estimate the relative risk and benefit of therapies in the 2 studies. Treatment risk was evaluated based on toxicity, and benefit was evaluated based on the length of survival in the absence of disease progression or AEs, by calculating the quality-adjusted time without symptoms or toxicity (Q-TWiST), the mean duration of toxicity prior to disease progression (TOX), and the time from disease progression until death or the last follow-up (REL).[3] TWiST was calculated as the difference in the mean durations of PFS and TOX.

An analysis of data from the ASCEND trial that used fixed utility values of 0.5 for TOX, 0.5 for REL, and 1 for TWiST showed that patients treated with acalabrutinib spent significantly less time in the TOX state and the REL state, and more time in the TWiST state, compared with patients treated with the rituximab combinations (Table 1). Q-TWiST was significantly prolonged with acalabrutinib monotherapy vs rituximab plus idelalisib or bendamustine

Table 1. Health State Analysis Among Patients in the ASCEND Trial

Health State	Estimated Difference Between the Treatment Arms (95% CI)	*P* Value
TOX	–0.73 (–1.24 to 0.24)	.004
REL	–2.25 (–3.50 to 1.60)	<.001
TWiST	3.58 (2.42 to 4.47)	<.001
Q-TWiST	1.96 (1.13 to 2.81)	<.001

Q-TWiST, quality-adjusted time without symptoms or toxicity; REL, time from disease progression until death or the last follow-up; TOX, mean duration of toxicity prior to disease progression; TWiST, the difference in the mean durations of progression-free survival and TOX.
Adapted from Seymour JF et al. ASH abstract 3722. *Blood*. 2021;138(suppl 1).[3]

Table 2. Health State Analysis Among Patients in the ELEVATE-RR Trial

Health State	Estimated Difference Between the Treatment Arms (95% CI)	*P* Value
Based on Grade 2 to 4 AEs		
TOX	–2.56 (–4.91 to –0.34)	.028
REL	0.37 (–1.82 to 2.59)	.751
TWiST	3.68 (0.82 to 6.34)	.010
Q-TWiST	2.58 (0.22 to 4.89)	.031
Based on AE Frequency of ≤10%		
TOX	–2.51 (–5.02 to –0.15)	.042
REL	0.37 (–1.82 to 2.60)	.749
TWiST	3.63 (0.75 to, 6.54)	.011
Q-TWiST	2.56 (0.19 to 4.83)	.031

AE, adverse events; Q-TWiST, quality-adjusted time without symptoms or toxicity; REL, time from disease progression until death or the last follow-up; TOX, mean duration of toxicity prior to disease progression; TWiST, the difference in the mean durations of progression-free survival and TOX.
Adapted from Seymour JF et al. ASH abstract 3722. *Blood*. 2021;138(suppl 1).[3]

(17.48 vs 15.52 months; difference, 1.96 months; *P*<.001).

In an analysis of the ELEVATE-RR trial—which calculated TOX based only on grade 3/4 AEs—the TOX, REL, TWiST, and Q-TWiST values were not significantly different between acalabrutinib vs ibrutinib (*P*>.05 for each). However, significant differences emerged between the 2 treatments when data sets for toxicity were narrowed to focus on particular events. For example, when grade 2 to 4 AEs were included in the TOX calculation, acalabrutinib was favored over ibrutinib in terms of Q-TWiST (Table 2; Q-TWiST difference, 2.58; *P*=.031). Similarly, when calculated based on the AEs that occurred in at least 10% of patients, Q-TWiST was again significantly better among patients treated with acalabrutinib compared with ibrutinib (Q-TWiST difference, 2.56 months; *P*=.031).

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SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib vs Bendamustine + Rituximab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Zanubrutinib is a second-generation BTK inhibitor that has improved target selectivity compared with ibrutinib.[1] Cohort 1 of the global, open-label phase 3 SEQUOIA trial evaluated zanubrutinib vs bendamustine plus rituximab in patients with treatment-naive CLL or small lymphocytic lymphoma (SLL).[2,3] Eligible patients met the iwCLL criteria for treatment. They were ages 65 years or older or were unsuitable for treatment with fludarabine, cyclophosphamide, and rituximab. Patients in arm A received zanubrutinib (160 mg, twice daily) until disease progression or unacceptable toxicity, and patients in arm B received 6 cycles of bendamustine (90 mg/m^2, days 1 and 2) plus rituximab (375 mg/m^2, day 1 of cycle 1, then 500 mg/m^2, cycles 2-6). Patients with del(17p) at screening were assigned to cohort 2/arm C, for treatment with zanubrutinib monotherapy, or to cohort 3/arm D, for treatment with zanubrutinib plus venetoclax. The primary endpoint was PFS by independent assessment.

The study randomly assigned 479 patients without del(17p) to arms A and B.[2] The patients' median age was 70 years (range, 66-75 years). Twenty-nine percent of patients in each arm had Binet stage C disease, and 29% to 31% had bulky disease (≥5 cm). In each arm, more than half of patients (52%-53%) had unmutated *IGHV*. Del(11q) was reported in 18% of patients in arm A and 19% of patients in arm B. After a median follow-up duration of approximately 26 months, the 24-month PFS was 85.5% with zanubrutinib

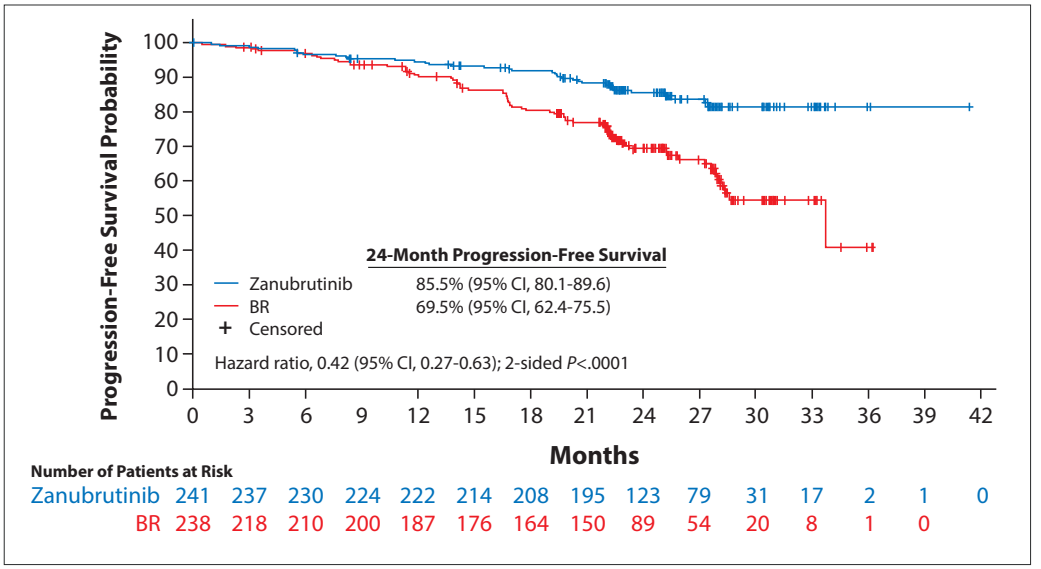

Figure 7. Median progression-free survival at 24 months in the phase 3 SEQUOIA trial, which compared zanubrutinib vs bendamustine plus rituximab in patients with treatment-naive chronic lymphocytic leukemia or small lymphocytic lymphoma. BR, bendamustine plus rituximab. Adapted from Tam CS et al. ASH abstract 396. *Blood*. 2021;138(suppl 1).[2]

vs 69.5% with bendamustine plus rituximab (HR, 0.42; 95% CI, 0.27-0.63; *P*<.0001; Figure 7). The median PFS was superior with zanubrutinib vs bendamustine plus rituximab in nearly all subgroups examined, including patients with bulky disease (HR, 0.52; 95% CI, 0.27-0.97), patients with unmutated *IGHV* (HR, 0.24; 95% CI, 0.24-0.43), and patients with del(11q) at baseline (HR, 0.21; 95% CI, 0.09-0.50). Zanubrutinib had a more favorable safety profile vs bendamustine plus rituximab, with fewer AEs of grade 3 or higher (53% vs 80%), fewer serious AEs (37% vs 50%), fewer AEs leading to dose reduction (8% vs 37%), and fewer AEs leading to discontinuation of study treatment (8% vs 14%).

Arm D of the SEQUOIA trial is evaluating zanubrutinib plus venetoclax in patients with treatment-naive CLL/SLL with del(17p), with a planned enrollment of 80 patients. Preliminary results were available from 35 enrolled patients. After a median follow-up of 9.7 months, 32 patients remained on study treatment. AEs of any grade were reported in 83% of patients, and serious AEs occurred in 11%. Among 13 patients (37%) with AEs of grade 3 or higher, the most common were neutropenia (n=4) and diarrhea (n=2). One patient with ongoing grade 2 atrial fibrillation at baseline experienced grade 3 atrial fibrillation while receiving the study medication. No tumor lysis syndrome was observed. Among 31 patients available for efficacy analysis, the ORR was 96.8%.

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Pirtobrutinib, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results From the Phase 1/2 BRUIN Study

Pirtobrutinib is a highly selective, reversible inhibitor of BTK.[1] Its pharmacokinetic properties allow for sustained inhibition of BTK throughout the dosing interval. Pirtobrutinib was designed to bind to BTK reversibly, and therefore inhibition of BTK is sustained even in the presence of high rates of BTK turnover. The phase 1/2 BRUIN study consisted of a dose-escalation phase, using a 3-plus-3 design, followed by expansion.[2] Intrapatient dose escalation was allowed, and cohort expansion was permitted based on acceptable safety. Eligible patients had relapsed or refractory CLL/SLL or another B-cell non-Hodgkin lymphoma, with active disease in need of treatment. The escalation and expansion doses of pirtobrutinib ranged from 25 mg to 300 mg, administered daily. The investigators selected 200 mg daily as the recommended phase 2 dose.

The efficacy population included 261 patients, whose median age was 69 years (range, 36-88 years). The median number of prior lines of therapy was 3 (range, 1-11). All of the patients had received prior therapy with a BTK inhibitor, and 88% had received an anti-CD20 antibody. Reasons for discontinuation of prior BTK inhibitor therapy included progressive disease (75%) and toxicity or other (25%). The most common cytogenetic feature was unmutated *IGHV* (84%). The median follow-up was 9.4 months (range, 0.3-27.4 months), and 74% of patients remained on pirtobrutinib.

Among 252 evaluable patients, the ORR was 68% (95% CI, 62%-74%), including complete responses in 1% (Figure 8). Despite prior treatment with a BTK inhibitor, nearly all patients had some reduction in tumor volume in response to pirtobrutinib.

ABSTRACT SUMMARY MAJIC: A Phase 3 Prospective, Multicenter, Randomized, Open-Label Trial of Acalabrutinib Plus Venetoclax vs Venetoclax Plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The multicenter, open-label, randomized phase 3 MAJIC trial is investigating venetoclax combined with either acalabrutinib (arm 1) or obinutuzumab (arm 2) in treatment-naive CLL/SLL patients (Abstract 1553). This noninferiority trial has a planned enrollment of approximately 750 adults with disease requiring treatment, an ECOG performance status of 2 or lower, and adequate organ function. Stratification factors include age, del(17p) and/or *TP53* mutation status, and *IGHV* mutation status. After 12 cycles of venetoclax combination therapy, patients with at least a PR and undetectable MRD of 10^{-5} will stop treatment. Patients with detectable MRD will continue combined treatment (arm 1) or venetoclax monotherapy (arm 2). Venetoclax will be administered for up to 24 months. The primary endpoint is investigator-assessed PFS. Key secondary endpoints include undetectable MRD at sequential time points, efficacy, safety, and quality of life.

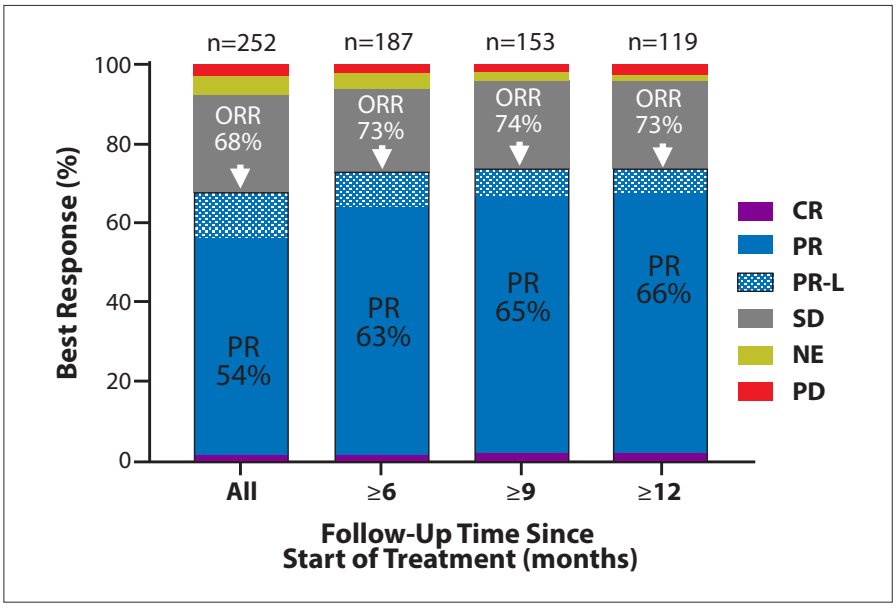

Figure 8. Best responses in an updated analysis of the phase 1/2 BRUIN study, which evaluated pirtobrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Adapted from Mato AR et al. ASH abstract 391. *Blood*. 2021;138(suppl 1).[2]

Moreover, reduction in tumor volume was observed in patients who had discontinued prior BTK inhibitor therapy, whether because of disease progression or poor tolerance, and in patients who had been previously treated with venetoclax. The median PFS was not estimable (95% CI, 17.0 months to not estimable). Among patients with prior exposure to a BTK inhibitor and venetoclax, the median PFS was 18 months (95% CI, 10.7 months to not estimable). Subgroup analysis showed favorable response rates, regardless of the prior therapy, the reason for prior discontinuation of BTK-inhibitor therapy, or the presence of unfavorable genetics. BTK C481 mutation status did not predict benefit from pirtobrutinib.

Pirtobrutinib was generally well tolerated. No dose-limiting toxicities were reported, and the maximum tolerated dose was not reached. The daily dose of pirtobrutinib was 200 mg or higher in 96% of patients. Only 1% of patients permanently discontinued pirtobrutinib therapy owing to treatment-related AEs. The most common grade 3/4 treatment-related AEs were neutropenia (8%) and fatigue (1%). Other grade 3/4 treatment-related AEs, each observed in less than 1% of patients, included diarrhea, rash, hemorrhage, and hypertension. Treatment-emergent atrial fibrillation/flutter of any grade was noted in 2% of patients.

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Matching-Adjusted Indirect Treatment Comparison of Acalabrutinib Alone or in Combination With Obinutuzumab vs Ibrutinib or Venetoclax Plus Obinutuzumab in Patients With Treatment-Naive Chronic Lymphocytic Leukemia

The ELEVATE-RR study compared acalabrutinib vs ibrutinib in previously treated CLL patients.[1] To estimate the efficacy and safety of acalabrutinib with or without obinutuzumab vs other therapies in treatment-naive patients with CLL, an unanchored, matching-adjusted, indirect treatment comparison (MAIC) analysis was performed based on patient data from the ELEVATE-TN, Alliance, and CLL-14 trials.[2-6]

Among patients treated with first-line acalabrutinib vs ibrutinib monotherapy, the PFS was similar (HR, 0.83; 95% CI, 0.50-1.37; *P*=.454), as was the median OS (HR, 0.69; 95% CI, 0.37-1.29; *P*=.247). In contrast, the MAIC analysis yielded a significant improvement with acalabrutinib plus obinutuzumab compared with ibrutinib monotherapy for the median PFS (HR, 0.48; 95% CI, 0.27-0.88; *P*=.017) and OS (HR, 0.41; 95% CI, 0.18-0.91; *P*=.029). Based on MAIC analysis, there was no significant difference with acalabrutinib monotherapy

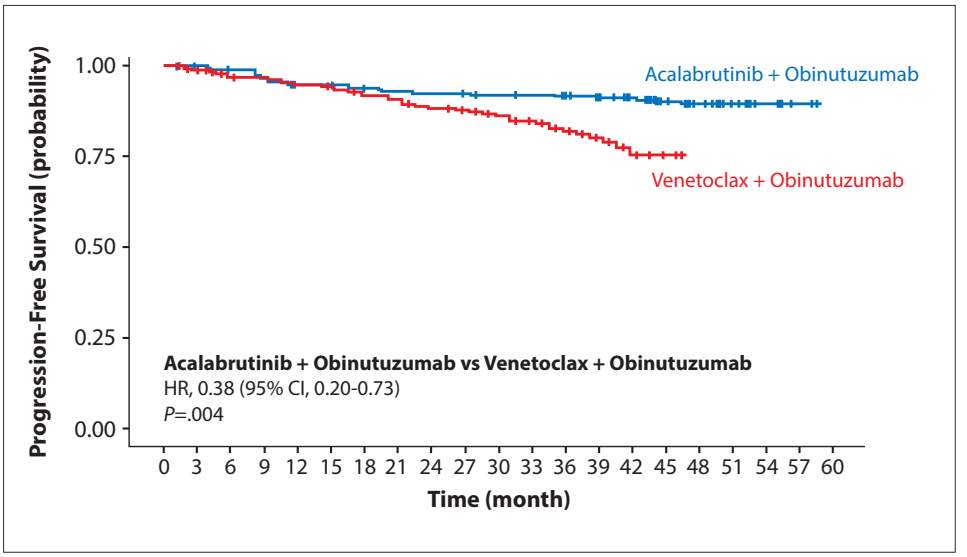

Figure 9. Progression-free survival among patients treated with acalabrutinib plus obinutuzumab or venetoclax plus obinutuzumab in an unanchored, matching-adjusted, indirect treatment comparison analysis of patient data from the ELEVATE-TN, Alliance, and CLL-14 trials. The comparator was the reference group in the HR calculation; an HR <1 is therefore in favor of acalabrutinib plus obinutuzumab. HR, hazard ratio. Adapted from Davids MS et al. ASH abstract 2633. *Blood*. 2021;138(suppl 1).[2]

compared with venetoclax plus obinutuzumab for PFS (HR, 0.96; 95% CI, 0.56-1.65; *P*=.883) or OS (HR, 0.99; 95% CI, 0.51-1.91; *P*=.974). However, patients treated with acalabrutinib plus obinutuzumab had a significantly prolonged PFS (HR, 0.38; 95% CI, 0.20-0.73; *P*=.004; Figure 9) and an improved OS (HR, 0.43; 95% CI, 0.19-0.99; *P*=.047).

MAIC analysis also showed a favorable safety profile for acalabrutinib monotherapy vs ibrutinib monotherapy and for acalabrutinib plus obinutuzumab vs ibrutinib monotherapy. Acalabrutinib monotherapy was associated with a significantly lower rate of grade 3 or higher AEs, including decreased neutrophil count (*P*<.001), decreased platelet count (*P*=.006), atrial fibrillation (*P*=.001), and hypertension (*P*<.001). The rates of these same AEs of grade 3 or higher were also lower in patients treated with acalabrutinib plus obinutuzumab compared with ibrutinib monotherapy (*P*<.05 for decreased neutrophil count, decreased platelet count, atrial fibrillation, and hypertension). Compared with venetoclax plus obinutuzumab, acalabrutinib with or without obinutuzumab yielded significantly lower rates of grade 3 or higher infusion-related reaction, leukopenia, neutropenia, and nonmelanoma skin cancer (*P*<.05 for each). In addition, acalabrutinib monotherapy was associated with lower rates of febrile neutropenia, secondary primary malignancy, and thrombocytopenia compared with venetoclax plus obinutuzumab (*P*<.05 for each).

ABSTRACT SUMMARY Phase II Study of Acalabrutinib and High-Frequency Low-Dose Subcutaneous Rituximab in Patients With Previously Untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

A single-arm, single-center phase 2 study investigated high-frequency/low-dose rituximab plus acalabrutinib in 37 treatment-naive CLL/SLL patients (Abstract 2640). After 6 cycles of combination therapy and 6 cycles of acalabrutinib monotherapy, patients with undetectable MRD stopped treatment, whereas those with detectable MRD continued with acalabrutinib monotherapy. Patients were a median age of 67 years, and 70% had at least 1 high-risk genetic feature. Grade 3/4 AEs included infection (13.5%), anemia (8.1%), and neutropenia (8.1%). There were 11 serious AEs. After a median follow-up of 14.0 months, the ORR was 100%, with 1 CR, 20 PRs, and 6 PRs with lymphocytosis. Although the ORR was high, only 1 patient achieved a CR, and none achieved MRD-negative CR. The low rate of CRs suggests that additional agents may be necessary to improve the efficacy of time-limited therapy in this patient setting.

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A Randomized Phase 3 Study of Venetoclax-Based Time-Limited Combination Treatments vs Standard Chemoimmunotherapy in Frontline Chronic Lymphocytic Leukemia of Fit Patients: First Co–Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

The phase 3 CLL13 trial compared 3 time-limited venetoclax combination regimens vs chemoimmunotherapy as first-line treatment in fit patients with CLL.[1] Enrolled patients had a Cumulative Illness Rating Scale (CIRS) score of at least 6 and a normal creatinine clearance rate. The trial excluded patients with a *TP53* mutation or del(17p) according to central screening. Stratification factors included age, disease stage, and geographic region. The chemoimmunotherapy regimen consisted of fludarabine, cyclophosphamide, and rituximab or bendamustine plus rituximab (arm 1; n=229). Venetoclax was combined with rituximab (arm 2; n=237), obinutuzumab (arm 3; n=229), or obinutuzumab and ibrutinib (arm 4; n=231). Undetectable MRD was defined as less than 10^{-4} based on 4-color flow cytometry.

The 926 patients were a median age of 61 years (range, 27-84 years) and had a median CIRS score of 2 (range, 0-7). More than half of patients (56%) had unmutated *IGHV* and 18% had del(11q). The median follow-up was 27.9 months. The rate of undetectable MRD at month 15 was 52.0% in arm 1, 57.0% in arm 2, 86.5% in arm 3, and 92.2% in arm 4 (Figure 10). The rate of undetectable MRD was significantly different in arm 3 vs arm 1 (*P*<.001), meeting the co–primary endpoint of undetectable MRD with obinutuzumab plus venetoclax vs chemoimmunotherapy. Rates of undetectable MRD in the peripheral blood were 37.1% in arm 1, 43.0% in arm 2, 72.5% in arm 3, and 77.9% in arm 4. The ORRs were similar across the 4 arms. However, the CR rate ranged from a low of 31% in arm 1 to a high of 61.9% in arm 4. Interim analysis of PFS was postponed owing to a low number of events.

In arms 1 to 4, AEs of grade 3 or higher of particular interest included febrile neutropenia, infections, and tumor lysis syndrome (Table 3). Grade 5 AEs occurred in 27 patients: 12 during treatment or through day 84 of the study, and 15 during the follow-up period. The most common grade 5 AEs occurring prior to day 84 were non–COVID-19 infection (n=4), secondary neoplasia other than

Table 3. Grade 3 or Higher Adverse Events of Special Interest

Adverse Event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)	Arm 4 (%)
Febrile Neutropenia	11.1	4.2	3.1	7.8
Infections	19.9	11.4	14.0	22.1
Tumor Lysis Syndrome	4.2	10.1	8.8	6.5

Adapted from Eichhorst B et al. ASH abstract 71. *Blood*. 2021;138(suppl 1).[1]

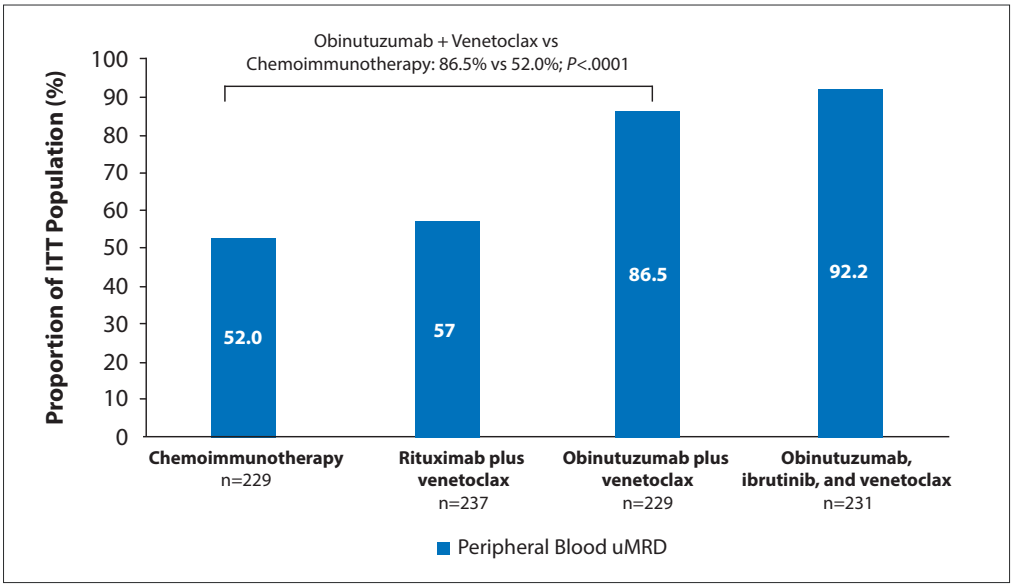

Figure 10. uMRD in the peripheral blood in the phase 3 CLL13 trial, which compared time-limited venetoclax combination regimens vs chemoimmunotherapy as first-line treatment in fit patients with chronic lymphocytic leukemia. ITT, intention to treat; uMRD, undetectable minimal residual disease. Adapted from Eichhorst B et al. ASH abstract 71. *Blood*. 2021;138(suppl 1).[1]

Richter transformation (n=4), and COVID-19 infection (n=2). The most common grade 5 AEs occurring after day 84 were secondary neoplasia other than Richter transformation (n=8), Richter transformation (n=3), and pneumonia (n=2). The rate of treatment discontinuation was less than 15% in all 3 venetoclax combination arms.

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Highlights in Chronic Lymphocytic Leukemia From the 63rd American Society of Hematology Annual Meeting and Exposition: Commentary

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Presentations in chronic lymphocytic leukemia (CLL) at the 63rd American Society of Hematology (ASH) annual meeting provided important insights into the management of patients with treatment-naive and relapsed/refractory disease. New data were presented for treatments such as the Bruton's tyrosine kinase (BTK) inhibitors acalabrutinib, zanubrutinib, and pirtobrutinib; ublituximab/umbralisib; and venetoclax combinations.

BTK Inhibitors

Acalabrutinib

Dr Wojciech Jurczak presented 3-year follow-up data for the randomized phase 3 ASCEND study, which evaluated acalabrutinib in relapsed/refractory CLL.[1,2] The trial compared acalabrutinib vs 1 of 2 options as a control: either rituximab plus idelalisib or bendamustine plus rituximab (BR). The initial results of this important trial led the US Food and Drug Administration (FDA) to approve acalabrutinib for the treatment of relapsed/refractory CLL.[1] Additionally, ASCEND was the first head-to-head randomized comparison of novel agents in this setting. The primary endpoint of the trial demonstrated superior progression-free survival for acalabrutinib over both of the controls.[1] Importantly, the updated analysis provided information about safety, showing that BTK inhibitors had superior safety vs phosphatidylinositol 3-kinase (PI3K) inhibitors.[2] The discontinuation rate for acalabrutinib owing to adverse events was low, at 20%. In contrast, adverse events led 60% of patients to discontinue idelalisib. This rate of discontinuation exceeded 70% when adding patients who stopped idelalisib owing to progressive disease. Importantly, these data can help clinicians make prospective sequencing decisions about whether BTK inhibitors should proceed a PI3K inhibitor. The 3-year follow-up analysis confirmed the initial findings. The progression-free survival advantage for acalabrutinib over the controls continues to widen with time.

The randomized phase 3 ELEVATE-RR trial was a head-to-head comparison of acalabrutinib vs ibrutinib in the relapsed/refractory setting in patients with high-risk features, including deletion 11q or deletion 17p.[3] The primary endpoint in the trial was noninferiority of acalabrutinib vs ibrutinib. Many of the key secondary endpoints focused on safety. At the ASH meeting, Dr John Seymour presented results from an expanded safety analysis.[4] The primary endpoint of the trial was met, in that acalabrutinib was noninferior to ibrutinib. Interestingly, there was an important safety signal for fewer cardiovascular events with acalabrutinib. Acalabrutinib was associated with lower rates of atrial fibrillation, hypertension, all-grade bleeding events, and arthralgias. Overall, data from the original report and the expanded safety data analysis showed that acalabrutinib appeared to be equally effective to ibrutinib, but with a far more favorable safety profile.[3,4] Based on these data and results of the ELEVATE-TN trial,[5] acalabrutinib is being increasingly used as a standard of care, in both the frontline and relapsed/refractory settings.

The multicenter, prospective, randomized phase 3 MAJIC trial is comparing acalabrutinib plus venetoclax vs venetoclax plus obinutuzumab in the frontline setting. Dr Matthew Davids presented this study as a trial-in-progress.[6] I am a co-leader of the trial, along with Dr Davids and Dr Jeff Sherman. The trial will compare 2 doublet regimens, using a minimal residual disease (MRD)-driven approach with 1 vs 2 years of therapy in both arms. The trial will perform noninferiority hypothesis testing to evaluate if both regimens are equally effective. This trial is important because it is addressing the question of which is the best doublet in the frontline setting. The trial will allow investigators to use MRD to make decisions about the duration of therapy, which is a new concept for the design of large, randomized clinical trials in CLL.

Zanubrutinib

The randomized phase 3 SEQUOIA trial compared zanubrutinib vs BR in the frontline setting.[7] This study is similar in design to the ALLIANCE trial, which compared ibrutinib with or without rituximab vs BR.[8] Several novel agent–based regimens have now been compared against chemoimmunotherapy in randomized trials.[8-10] The SEQUOIA study was designed to allow possible regulatory approval of zanubrutinib in the frontline setting. This BTK inhibitor demonstrated a favorable adverse event profile, as well as superior progression-free survival vs BR in all subgroups. The results are similar to those reported with ibrutinib (vs BR) in the ALLIANCE trial,[8] and they may lead to the FDA approval of zanubrutinib in the frontline setting. The study provided further confirmatory evidence supporting zanubrutinib as a next-generation BTK inhibitor that is active and safe in both the frontline and relapsed/refractory settings.

Dr Alessandra Tedeschi presented early results from one of many arms of the phase 3 SEQUOIA trial, which is evaluating zanubrutinib (BGB-3111) in patients with treatment-naive CLL or small lymphocytic leukemia.[11] These data are for a relatively small group of patients (<100) with deletion 17p who received zanubrutinib plus venetoclax. Treatment led to a high overall response rate and durable remissions. The safety profile appeared favorable as compared with safety data for ibrutinib plus venetoclax from the CAPTIVATE and GLOW trials.[12,13] This preliminary report did not provide data for survival or MRD.

In another report of data from the SEQUOIA trial, zanubrutinib monotherapy in patients with deletion 17p was effective.[14] It is likely that monotherapy will have fewer side effects than a combination regimen. The question now is whether patients with poor-risk features should receive a combination of 2 novel agents in a fixed-duration or MRD-driven strategy, or if monotherapy with a BTK inhibitor should be considered the standard of care.

Pirtobrutinib

Pirtobrutinib is a next-generation, highly selective, noncovalent BTK inhibitor under investigation in CLL. Pirtobrutinib was designed to be highly selective for BTK, but also to bind in a different location on that target in order to overcome resistance.[15] The overall design was meant to be highly effective in both wild-type and cysteine 481–mutated disease, while also being well tolerated based on the high specificity for BTK. The phase 1/2 BRUIN trial examined doses of pirtobrutinib between 25 mg and 300 mg once daily in patients with CLL and B-cell lymphomas.[16] The trial followed a standard 3-plus-3 design. I presented updated results for 252 patients with CLL who had received previous treatment with a covalent BTK inhibitor (100%). Other common previous therapies included venetoclax in 41% and PI3K inhibitors in 20%. Most patients had also received chemoimmunotherapy.

Pirtobrutinib was extremely well tolerated. Only 1% of patients discontinued treatment owing to adverse events. The drug was active, with an overall response rate of 68%. For the entire study cohort in this analysis, the median progression-free survival was not reached. Among patients previously exposed to a BTK inhibitor and venetoclax, the median progression-free survival was 18 months (median of 5 prior therapies). Importantly, the BRUIN study demonstrated that cysteine 481 mutational status had no impact on progression-free survival in patients who discontinue a covalent BTK inhibitor owing to disease progression.[16] Pirtobrutinib is an important addition to therapy in terms of activity and safety profile. The drug addresses an unmet need for patients who develop progressive disease during treatment with covalent BTK inhibitors and for patients who are double-exposed to a BTK inhibitor and venetoclax.

Ublituximab/Umbralisib

Dr Lindsey Roeker presented results from a phase 2 study evaluating the addition of ublituximab/umbralisib (U2) to ibrutinib in patients with CLL.[17] The study followed an MRD-driven, time-limited approach. Patients with CLL are now being offered combination therapies consisting of doublets and triplets. Combination therapies are likely important for certain patients with high-risk disease and those with an inadequate response to targeted agents administered as monotherapies. However, this strategy can also lead to overtreatment of many patients. The study evaluated an "add-on" approach, in which the combination of umbralisib plus ublituximab was added to ibrutinib. This regimen was administered in the frontline or relapsed/refractory settings to patients who had received ibrutinib for at least 6 months, with the goal of inducing a deeper remission to allow discontinuation of the drug. The primary endpoint was the rate of undetectable MRD. Key secondary endpoints included safety, time to undetectable MRD, and progression-free survival.

There were several take-home messages from the trial. The results showed that the U2 combination could be successfully added to ibrutinib from a safety perspective.[17] In more than 70% of patients, the treatment induced undetectable MRD in the peripheral blood with a sensitivity of 10^{-4}. When patients discontinued treatment, they were able to maintain durable remissions for prolonged periods. Among the 27 patients evaluable for efficacy, only 1 had developed progressive disease at the time of the report. Overall, this study demonstrated proof of concept that an "add-on" approach for a PI3K inhibitor plus a BTK inhibitor can induce undetectable MRD and durable remissions. The study also provided additional evidence for the use of a venetoclax-free triple combination regimen, which could be viewed as a time-limited, MRD-driven approach.

Venetoclax Combinations

Dr Barbara Eichhorst provided results of the phase 3 CLL13 trial, a 4-arm comparison of venetoclax plus ibrutinib vs venetoclax vs rituximab vs venetoclax plus obinutuzumab vs chemoimmunotherapy in the frontline setting.[18] It should be noted that the report provided extremely preliminary data. This trial found that the venetoclax-based arms were superior to chemoimmunotherapy in terms of depth of remission. Another important finding was that rates of undetectable MRD appeared higher with obinutuzumab than rituximab. The take-away message from this trial is that when venetoclax is combined with an anti-CD20 monoclonal antibody, the latter should be obinutuzumab based on the depth of remission. It was interesting to see this comparison of multiple venetoclax-based arms in the frontline setting. Data are still lacking for safety and progression-free survival.

Dr Paolo Ghia presented 2-year post-randomization data from the CAPTIVATE study.[19] This important study was the first attempt at an MRD-driven approach for treatment with ibrutinib plus venetoclax. Patients received 3 months of ibrutinib followed by 12 months of combination therapy with ibrutinib plus venetoclax. Patients were then randomly assigned to treatment based on their MRD status. Patients with undetectable MRD were randomly assigned to either continue treatment with ibrutinib or receive placebo. Patients with detectable MRD were randomly assigned to receive ibrutinib or continued therapy with ibrutinib plus venetoclax. The primary endpoint was comparison of 12-month disease-free survival in the undetectable MRD cohort. The presentation by Dr Ghia provided results for 24-month disease-free survival in patients with confirmed undetectable MRD.[19] A previous report showed that there was no statistically significant difference in 12-month disease-free survival between the ibrutinib vs placebo arms.[12] There were no new cases of disease progression in either arm. This analysis again supports the earlier data showing that if a patient achieves undetectable MRD after 12 months of combination therapy with ibrutinib plus venetoclax, there is likely no benefit for continuing ibrutinib alone as maintenance therapy.

An analysis of patients with detectable MRD showed that continued treatment with ibrutinib plus venetoclax, but not ibrutinib alone, deepened response.[19] There might be a subset of patients with detectable MRD in whom continued venetoclax-based therapy might deepen responses and possibly improve progression-free survival.

Disclosure

Dr Mato has provided services to AbbVie, Adaptive Biotechnologies Corp, AstraZeneca, Bio Ascend, Bristol Myers Squibb, Curio Science LLC, Genentech, Janssen Biotech, Inc, Loxo Oncology, Merck & Co Inc, Octapharma, OncLive, Pfizer, Pharmacyclics, TG Therapeutics, and prIME Oncology.

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