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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 62nd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the All-Virtual 62nd ASH Meeting and Exposition • December 5-8, 2020

Special Reporting on:

- Updated Safety and Efficacy Results From a Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab for Frontline Treatment of Chronic Lymphocytic Leukemia
- Clonal Dynamics After Venetoclax-Obinutuzumab Therapy: Novel Insights From the Randomized Phase 3 CLL14 Trial
- Acalabrutinib in Combination With Venetoclax and Obinutuzumab or Rituximab in Patients With Treatment-Naive or Relapsed/Refractory Chronic Lymphocytic Leukemia
- LOXO-305, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results From the Phase 1/2 BRUIN Study
- Acalabrutinib vs Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia: ASCEND Final Results
- Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 1-Year Disease-Free Survival Results From the MRD Cohort of the Phase 2 CAPTIVATE Study
- Umbralisib Plus Ublituximab (U2) Is Superior to Obinutuzumab Plus Chlorambucil (O+Chl) in Patients With Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: Results From the Phase 3 UNITY-CLL Study
- TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel in Combination With Ibrutinib for Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Continued Long-Term Responses to Ibrutinib + Venetoclax Treatment for Relapsed/Refractory CLL in the Blood Cancer UK TAP CLARITY Trial

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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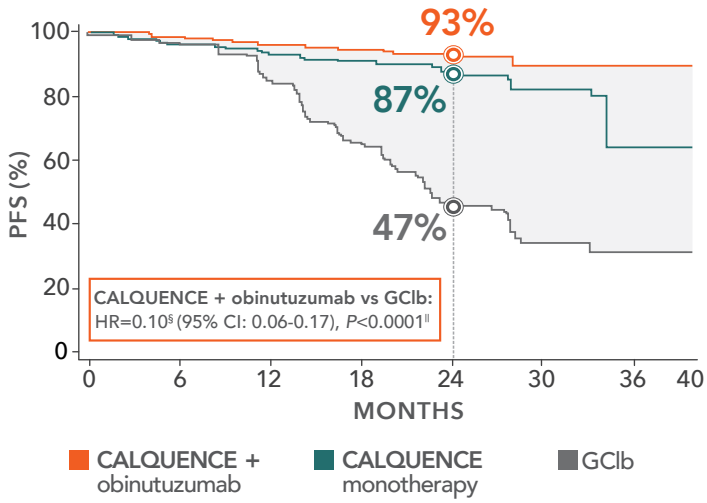
CALQUENCE
(acalabrutinib) 100 mg capsules

CALQUENCE CONFIDENCE

UNPRECEDENTED PFS: 90% RISK REDUCTION IN DISEASE PROGRESSION OR DEATH WITH CALQUENCE + OBINUTUZUMAB vs GClb

At median 28.3-month follow-up (range: 0.0 to 40.8 months), median PFS was not reached with CALQUENCE + obinutuzumab vs 22.6 months (95% CI: 20-28) with GClb in patients with previously untreated CLL.*[1]

IRC-ASSESSED PROGRESSION-FREE SURVIVAL†[1,2]



93% estimated PFS at 24 months for CALQUENCE + obinutuzumab‡[2]

CALQUENCE monotherapy[1]

- 80% relative risk reduction in disease progression or death vs GClb (HR=0.20§ [95% CI: 0.13-0.30], *P*<0.0001‖)
- Median PFS was not reached (95% CI: 34-NE) vs 22.6 months (95% CI: 20-28) with GClb

Study Design[1,2]

ELEVATE-TN was a Phase 3, open-label, randomized, multicenter trial in patients with previously untreated CLL (N=535). Patients were randomized 1:1:1 to receive either CALQUENCE + obinutuzumab (n=179), CALQUENCE monotherapy (n=179), or GClb (n=177). Patients in the CALQUENCE arms received 100 mg approximately every 12 hours until disease progression or unacceptable toxicity. The primary comparison was PFS between the CALQUENCE + obinutuzumab and GClb arms. PFS for CALQUENCE monotherapy vs GClb was a secondary endpoint in the study.

*Per 2008 International Workshop on CLL criteria.[1]
†At the time of analysis, the number of events in each arm was 14 (8%) for CALQUENCE + obinutuzumab, 26 (15%) for CALQUENCE monotherapy, and 93 (53%) for GClb.[1]
‡Estimated 24-month PFS: CALQUENCE + obinutuzumab, 93% (95% CI: 87-96); CALQUENCE monotherapy, 87% (95% CI: 81-92); GClb, 47% (95% CI: 39-55).[2]
§Based on a stratified Cox proportional-hazards model. Both hazard ratios are compared with the GClb arm.[1]
‖Based on a stratified log-rank test, with an alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method.[1]
CI=confidence interval; CLL=chronic lymphocytic leukemia; GClb=obinutuzumab + chlorambucil; HR=hazard ratio; IRC=Independent Review Committee; NE=not estimable; PFS=progression-free survival.

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies

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

Atrial Fibrillation and Flutter

Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (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 previously untreated CLL exposed to CALQUENCE, fatal adverse reactions that occurred in the absence of disease progression and with onset within 30 days of the last study treatment were reported in 2% for each treatment arm, most often from infection. Serious adverse reactions were reported in 39% of patients in the CALQUENCE plus obinutuzumab arm and 32% in the CALQUENCE monotherapy arm, most often due to events of pneumonia (7% and 2.8%, respectively).

IN PREVIOUSLY UNTREATED CLL

90% RISK REDUCTION IN DISEASE PROGRESSION OR DEATH[‡]

CALQUENCE + obinutuzumab vs obinutuzumab + chlorambucil
HR=0.10 (95% CI: 0.06-0.17), *P*<0.0001

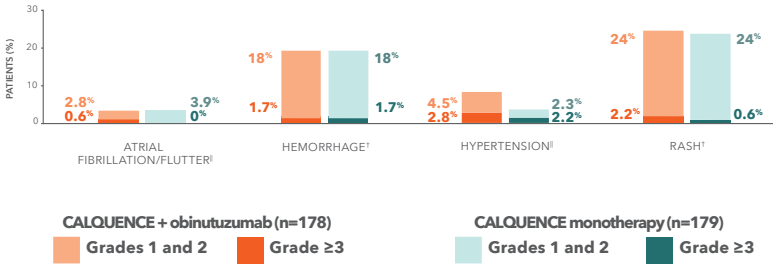
TO LEARN MORE, VISIT **CALQUENCEhcp.com**

SAFETY AND TOLERABILITY CONSISTENT WITH THE ESTABLISHED PROFILE OF CALQUENCE

*COMMON ADVERSE REACTIONS (≥15%, ANY GRADE) WITH CALQUENCE IN ELEVATE-TN**[1]

	CALQUENCE + obinutuzumab (n=178)		CALQUENCE monotherapy (n=179)		GClb (n=169)	
Adverse reaction	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Infection[†]	69	22[‡]	65	14[‡]	46	13[‡]
Upper respiratory tract infection[†]	39	2.8	35	0	17	1.2
Lower respiratory tract infection[†]	24	8	18	4.5	7	1.8
Urinary tract infection	15	1.7	15	2.8	5	0.6
Neutropenia[†]	53	37	23	13	78	50
Anemia[†]	52	12	53	10	54	14
Thrombocytopenia[†]	51	12	32	3.4	61	16
Lymphocytosis[†]	12	11	16	15	0.6	0.6
Headache	40	1.1	39	1.1	12	0
Dizziness	20	0	12	0	7	0
Diarrhea	39	4.5	35	0.6	21	1.8
Nausea	20	0	22	0	31	0
Musculoskeletal pain[†]	37	2.2	32	1.1	16	2.4
Arthralgia	22	1.1	16	0.6	4.7	1.2
Fatigue[†]	34	2.2	23	1.1	24	1.2
Bruising[†]	31	0	21	0	5	0
Rash[†]	26	2.2	25	0.6	9	0.6
Hemorrhage[†]	20	1.7	20	1.7	6	0

SELECT ADVERSE REACTIONS FOR CALQUENCE[§1,2]



Other clinically relevant adverse reactions (<15%, any grade) in recipients of CALQUENCE (CALQUENCE + obinutuzumab and as monotherapy) included neoplasms: second primary malignancy (10%), including non-melanoma skin cancer (5%); infection: herpesvirus infection (6%); and cardiac disorders: atrial fibrillation or flutter (3.6%), hypertension (5%).[1]

Select non-hematologic laboratory abnormalities (≥15%, any grade) that were new or worsening from baseline in patients receiving CALQUENCE included increases in uric acid, alanine aminotransferase, aspartate aminotransferase, and bilirubin.[1]

*The median duration of exposure to CALQUENCE in the CALQUENCE + obinutuzumab and CALQUENCE monotherapy arms was 27.7 months (range: 0.3 to 40 months).[1]

[†]Includes multiple adverse drug reaction terms (see full Prescribing Information).[1]

[‡]Includes 3 fatal cases in the CALQUENCE + obinutuzumab arm, 3 fatal cases in the CALQUENCE monotherapy arm, and 1 fatal case in the GClb arm.[1]

[§]Infusion-related reactions were reported in 14% of patients in the CALQUENCE + obinutuzumab arm and 40% of patients in the GClb arm.[2]

[‖]There were no events of Grade 4 or 5 atrial fibrillation or hypertension reported.[3]

IMPORTANT SAFETY INFORMATION (Cont'd)

Adverse reactions led to CALQUENCE dose reduction in 7% and 4% of patients in the CALQUENCE plus obinutuzumab arm (N=178) and CALQUENCE monotherapy arm (N=179), respectively. Adverse events led to discontinuation in 11% and 10% of patients, respectively. Increases in creatinine 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.

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. CALQUENCE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **2.** Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial [published correction appears in *Lancet*. 2020;395(10238):1694]. *Lancet*. 2020;395(10232):1278-1291. **3.** Data on File, REF-78409. AstraZeneca Pharmaceuticals LP.

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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Updated Safety and Efficacy Results From a Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab for Frontline Treatment of Chronic Lymphocytic Leukemia

Acalabrutinib is a second-generation inhibitor of Bruton tyrosine kinase (BTK) that binds covalently to its target.[1] The drug has yielded promising response rates with a manageable safety profile in phase 1/2 trials of patients with chronic lymphocytic leukemia (CLL). Acalabrutinib was evaluated in combination with venetoclax and obinutuzumab in an investigator-initiated phase 2 study of treatment-naive patients with CLL/small lymphocytic lymphoma (SLL).[2,3] The trial initially enrolled patients with mutated or wild-type *TP53*. The protocol was later amended to restrict enrollment to patients with CLL who had the *TP53* mutation; these patients were enrolled in a new cohort. All patients required treatment, based on criteria from the International Workshop on CLL (iwCLL) 2018 guidelines.[4] The patients had adequate levels of absolute neutrophil and platelet counts, plus adequate hepatic and renal function. To make the 3-drug combination more tolerable, treatment with acalabrutinib, obinutuzumab, and venetoclax was started sequentially. Cycle 1 consisted of acalabrutinib monotherapy at 100 mg, twice daily. Obinutuzumab was added at the standard dose for 2 cycles. Venetoclax was then added over the course of 4 weeks, with a starting dose of 20 mg on day 1 of cycle 4, then 50 mg on day 2 of cycle 4, followed by weekly ramp-up to a dose of 400 mg daily. After a total of 4 cycles of the 3-drug regimen, patients received acalabrutinib plus obinutuzumab for cycles 8 to 15. The patients were assessed for response after 15 cycles. Patients with a complete response (CR) and undetectable minimal residual disease (MRD) in the bone marrow after cycle 15 could discontinue therapy. Patients who had a partial response (PR) or a CR with detectable MRD continued with acalabrutinib plus venetoclax through cycle 24, at which point the responses were assessed again. Patients with undetectable bone marrow MRD discontinued treatment, while the other patients continued to receive acalabrutinib and venetoclax. Responses were assessed based on iwCLL 2018 guidelines, with central testing of MRD by 8-color flow cytometry. The primary endpoint was the rate of CR with undetectable bone marrow MRD by day 1 of cycle 16.

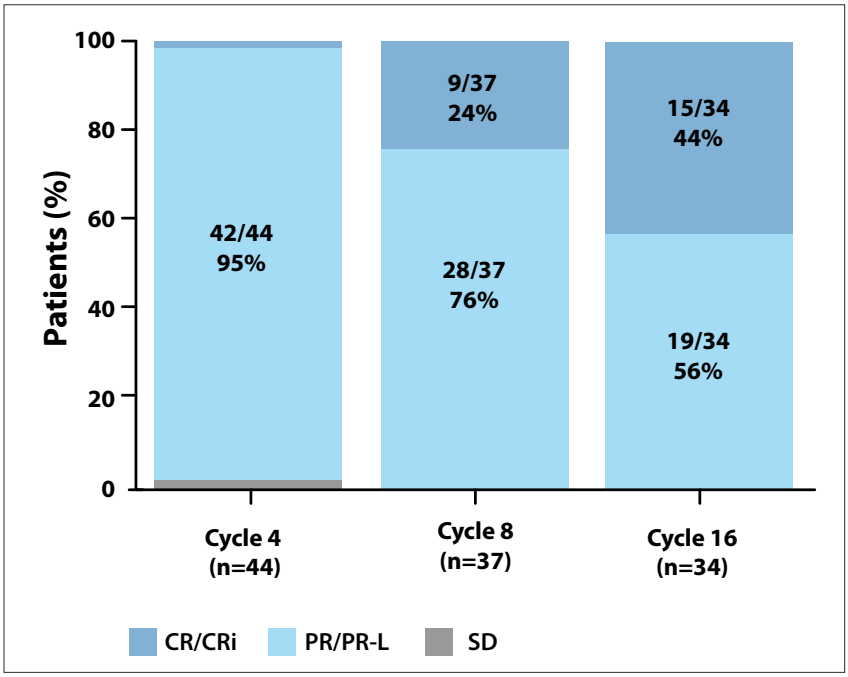

Figure 1. Response among patients with chronic lymphocytic leukemia who received frontline treatment with acalabrutinib, venetoclax, and obinutuzumab in a phase 2 trial. CR, complete response; CRi, complete response with incomplete hematologic recovery; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Adapted from Davids MS et al. ASH abstract 2219. *Blood*. 2020;136(suppl 1).[2]

The trial enrolled 44 patients. Their median age was 63 years (range, 41-78 years), and their Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1. More than half of the patients (54.5%) had Rai stage III/IV disease. The most common genetic abnormalities included *TP53* aberrancy in 38.6%, 13q deletion in 45.5%, and 11q deletion (del[11q]) in 27.3%.

The objective response rate (ORR) at the end of 15 treatment cycles was 100% (with a CR rate of 56%; Figure 1). Among the 10 patients with a *TP53* abnormality, 4 had a CR. The rate of undetectable bone marrow MRD was 76.5% (26/34; Figure 2) among all patients and 70% (7/10) among patients with *TP53* aberrancy.

Serious adverse events (AEs) included grade 4 neutropenia in 4 patients and grade 4 hyperkalemia in 1 patient, as well as 1 case each of grade 3 elevated cardiac troponin 1 and grade 3 lung infection. Infusion-related reactions occurred in 11 patients (25%),

including 1 grade 3 event. Grade 1/2 hypertension was observed in 5 patients (11%). One patient developed grade 3 atrial fibrillation during cycle 9, and 2 patients developed grade 3 laboratory tumor lysis syndrome after initiation of obinutuzumab therapy and prior to the addition of venetoclax. The risk of tumor lysis syndrome was reduced by administering 3 cycles of acalabrutinib and obinutuzumab prior to the addition of venetoclax.

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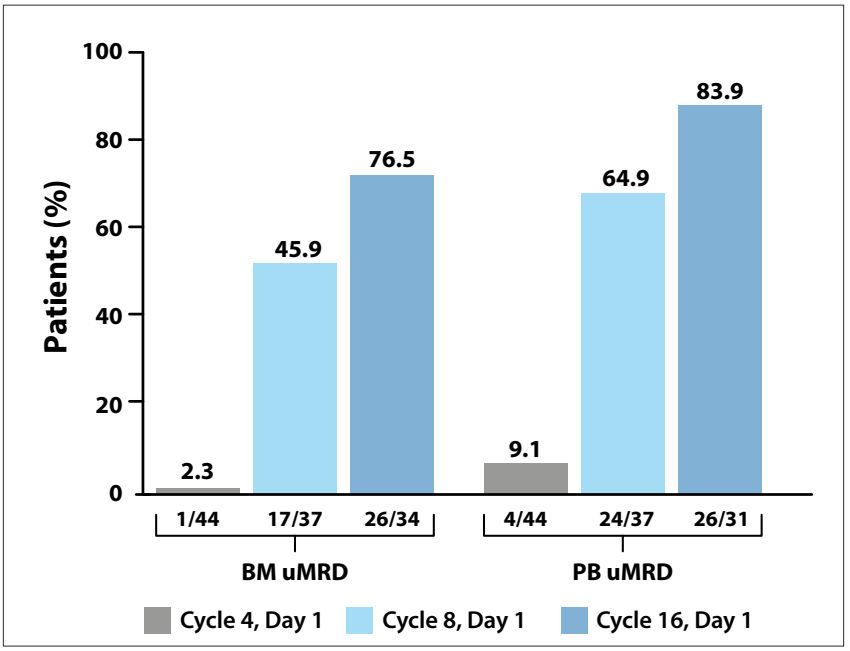

Figure 2. Measurable residual disease in the intention-to-treat population of a phase 2 trial evaluating frontline treatment with acalabrutinib, venetoclax, and obinutuzumab in patients with chronic lymphocytic leukemia. BM, bone marrow; PB, peripheral blood; uMRD, undetectable minimal residual disease. Adapted from Davids MS et al. ASH abstract 2219. *Blood.* 2020;136(suppl 1).[2]

Clonal Dynamics After Venetoclax-Obinutuzumab Therapy: Novel Insights From the Randomized Phase 3 CLL14 Trial

Achievement of undetectable MRD correlates with time to relapse and is an important goal during treatment with CLL regimens of fixed duration.[1] Evaluation of MRD was a key secondary endpoint of the open-label phase 3 CLL14 trial.[2,3] The trial enrolled 445 patients with treatment-naive CLL and coexisting medical conditions, as indicated by a cumulative illness rating scale score higher than 6 and/or a creatinine clearance rate of less than 70 mL/min. The intention-to-treat population included 432 patients. These patients were randomly assigned to treatment with 6 cycles of venetoclax plus obinutuzumab, followed by 6 cycles of venetoclax, or 6 cycles of chlorambucil plus obinutuzumab, followed by 6 cycles of chlorambucil. The primary endpoint was progression-free survival (PFS). After a median follow-up of 28.1 months, the estimated 24-month PFS was 88.2% with venetoclax plus obinutuzumab vs 64.1% with chlorambucil plus obinutuzumab (hazard ratio [HR], 0.35; 95% CI, 0.23-0.53; $P<.001$). At the end of treatment, the rate of undetectable MRD was 74% vs 32%, respectively. The median PFS continued to improve in the venetoclax arm with longer follow-up.[4]

In order to calculate a patient-specific clonal growth rate, MRD was evaluated in peripheral blood samples taken at the end of treatment and at subsequent time points. An exponential regression model was used to estimate each patient's clonal doubling time. The analysis included patients who did not experience disease progression prior to the end of treatment and who had at least 2 available MRD measurements taken after the end of treatment. MRD was analyzed by next-generation sequencing with a limit of quantification of less than 10^{-6}. At the end of treatment, the proportion of patients with undetectable MRD was 40% in the venetoclax arm vs 6% in the control arm. Approximately one-third of patients in the venetoclax combination arm experienced a deepening of MRD response during the 6 cycles of venetoclax monotherapy. At the end of 6 cycles of combination treatment, 20 patients in the venetoclax arm were MRD-positive. Between the initiation of treatment cycle 7 and

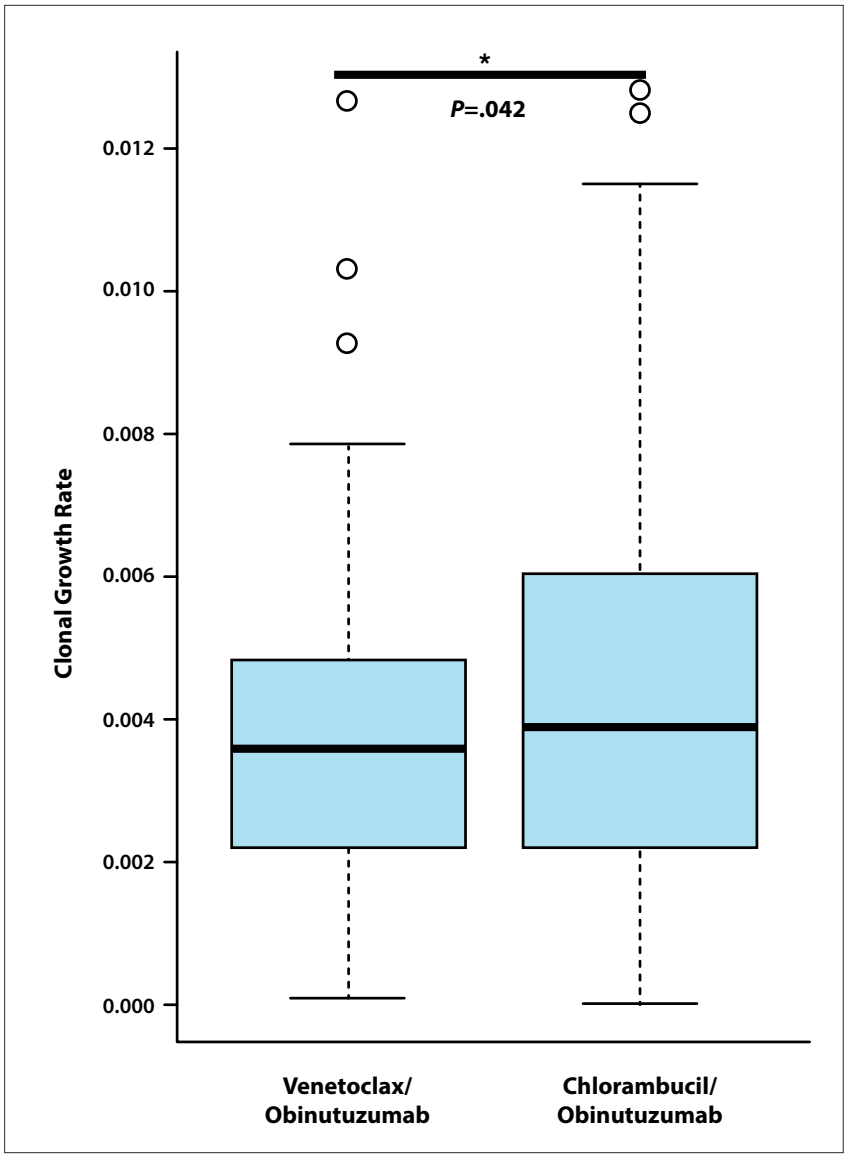

Figure 3. The clonal growth rate among patients treated with venetoclax plus obinutuzumab or chlorambucil plus obinutuzumab in the CLL14 trial. Adapted from Al-Sawaf O et al. ASH abstract 127. *Blood.* 2020;136(suppl 1).[3]

3-month follow-up, approximately half of these patients experienced positive growth of their residual CLL cells. The remaining patients experienced a reduction in MRD, and thus could potentially achieve undetectable MRD with extended venetoclax monotherapy. The clonal growth rate was 0.0037 with venetoclax plus obinutuzumab vs 0.0043 with chlorambucil plus obinutuzumab (*P*=.042; Figure 3). A higher growth rate was observed in patients with high-risk disease features, such as older age (≥65 years), a high score on the CLL International Prognostic Index, unmutated immunoglobulin heavy chain variable (*IGHV*) region, and other genetic variants. In approximately 20% of patients in the venetoclax arm, MRD results were below the limit of quantification, indicating very deep remission

With a median observation of 52.4 months, the median PFS was not reached with venetoclax/obinutuzumab vs 36.4 months with chlorambucil/obinutuzumab (HR, 0.33; 95% CI, 0.25-0.45; *P*<.0001). The 4-year rate of PFS was 74.0% with venetoclax plus obinutuzumab vs 35.4% with chlorambucil plus obinutuzumab (HR, 0.33; 95% CI, 0.25-0.45; *P*<.0001. The 4-year time-to-next-treatment was 81.08% vs 9.9%, respectively (HR, 0.46; 95% CI, 0.32-0.65; *P*<.0001). Four-year overall survival was similar for both arms (85.3% with venetoclax vs 83.1% with chlorambucil; HR, 0.85; 95% CI, 0.54-1.35; *P*=.4929).

The study investigators concluded that individual clonal growth rates can be used to estimate growth dynamics after fixed-duration treatment with venetoclax plus obinutuzumab. The lower rate of clonal growth reported after treatment with venetoclax plus obinutuzumab vs chlorambucil plus obinutuzumab suggests that the former treatment was associated with more effective eradication of MRD and modulation of clonal growth. In approximately 20% of patients treated with venetoclax plus obinutuzumab, no clonal growth was measurable, indicating deep remissions. These remissions led to a sustained benefit in PFS lasting several years after completion of treatment.

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Acalabrutinib in Combination With Venetoclax and Obinutuzumab or Rituximab in Patients With Treatment-Naive or Relapsed/Refractory Chronic Lymphocytic Leukemia

The phase 1b ACE-CL-003 trial evaluated acalabrutinib and venetoclax plus either obinutuzumab or rituximab in patients with CLL.[1,2] Cohort analyses were performed to assess the efficacy and safety of acalabrutinib, venetoclax, and rituximab (AVR) in patients with relapsed or refractory CLL and of acalabrutinib, venetoclax, and obinutuzumab (AVO) in patients with treatment-naive CLL. All patients had intermediate-risk or high-risk CLL and an ECOG performance status of 0 to 2. Twelve patients who had received at least 1 prior systemic therapy were enrolled into the AVR cohort and 12 treatment-naive patients were enrolled into the AVO cohort. Both cohorts received acalabrutinib (100 mg, twice daily) for up to 24 cycles plus venetoclax (ramped up to 400 mg on day 1 of cycle 4) until the end of cycle 15. According to their cohort, patients received 9 infusions of rituximab (375 mg/m^2) or standard dosing of obinutuzumab during cycles 2 to 7. The primary endpoint was safety. The median age was 66.5 years in the AVR cohort vs 60.5 years in the AVO cohort. Patients in the AVR cohort had received a median of 1 prior therapy (range, 1-3). Bulky disease was present in 25% of patients in the AVR cohort vs 58% in the AVO cohort. Other baseline characteristics were generally similar for the patient groups. The median follow-up was 27.7 months for the AVR cohort vs 26.0 months for the AVO cohort.

After 16 treatment cycles, the ORR was 92% (95% CI, 62%-100%) in patients who were previously treated at baseline and 100% (95% CI, 74%-100%) in treatment-naive patients. In each cohort, 50% of patients achieved a CR or CR with incomplete hematologic recovery (CRi). The median duration of response, PFS, and overall survival were not reached in either cohort. The estimated 18-month rates of PFS and overall survival were 100% for both cohorts. Pharmacokinetic findings with acalabrutinib, its active metabolite, and venetoclax were similar to those observed with monotherapy. The rate of undetectable MRD (≤0.01%) for both cohorts combined was 71% (Figure 4). By day 1 of cycle 10 and/or day 1 of cycle 16, only 1 of 12 patients (8%) remained MRD-positive in the peripheral blood in both cohorts.

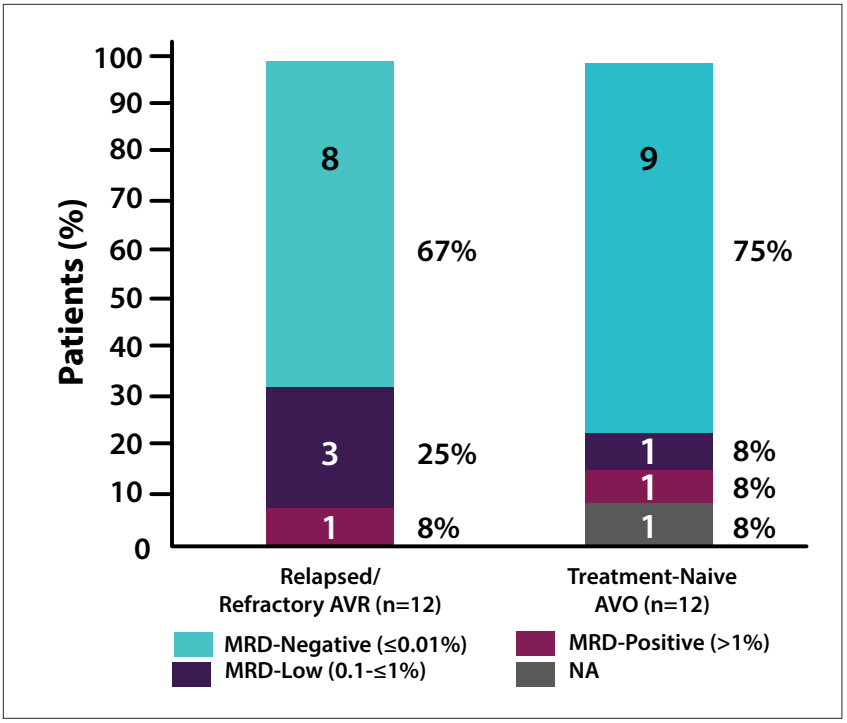

Figure 4. Status of minimal residual disease in the peripheral blood at cycle 10 among patients with chronic lymphocytic leukemia who received acalabrutinib, venetoclax, and obinutuzumab or acalabrutinib, venetoclax, and rituximab in the phase 1b ACE-CL-003 trial. AVO, acalabrutinib, venetoclax, and obinutuzumab; AVR, acalabrutinib, venetoclax, and rituximab; MRD, minimal residual disease; NA, not available. Adapted from Woyach JA et al. ASH abstract 1312. *Blood*. 2020;136(suppl 1).[2]

The most common AEs of any grade included headache, nausea, and diarrhea in the AVR cohort and diarrhea, upper respiratory tract infection, and headache in the AVO cohort. Nine patients overall had grade 1/2 infusion-related reactions. Decreased neutrophil counts of grade 3 or higher were observed in 1 patient (8%) with relapsed or refractory disease at baseline and in 6 patients (50%) with treatment-naive disease at baseline. No cases of ventricular arrhythmia, Richter transformation, or death were reported.

Serious AEs of grade 3 or higher were noted in 2 patients (17%) in the AVR cohort and 4 patients (33%) in the AVO cohort. Infections of grade

3 or higher were observed among 3 patients (25%) in the AVO cohort. No cases of tumor lysis syndrome were observed in either cohort.

References

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LOXO-305, A Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results From the Phase 1/2 BRUIN Study

Among patients with CLL, treatment with BTK inhibitors might be discontinued not only because of AEs, but also because acquired mutations in *BTK* or *PLCG2* may lead to drug resistance. Genetic analysis of CLL patients treated with ibrutinib in 4 prospective studies showed a discontinuation rate of 54% among patients with relapsed or refractory disease at study entry, and resistance mutations were common among patients who relapsed after treatment with ibrutinib.[1] Mutations in BTK residue C481 attenuate the activity of covalent BTK inhibitors, and *C481* mutations are the most common reason for CLL progression after treatment with a covalent BTK inhibitor.[1-8]

LOXO-305 is a reversible BTK inhibitor with nanomolar potency

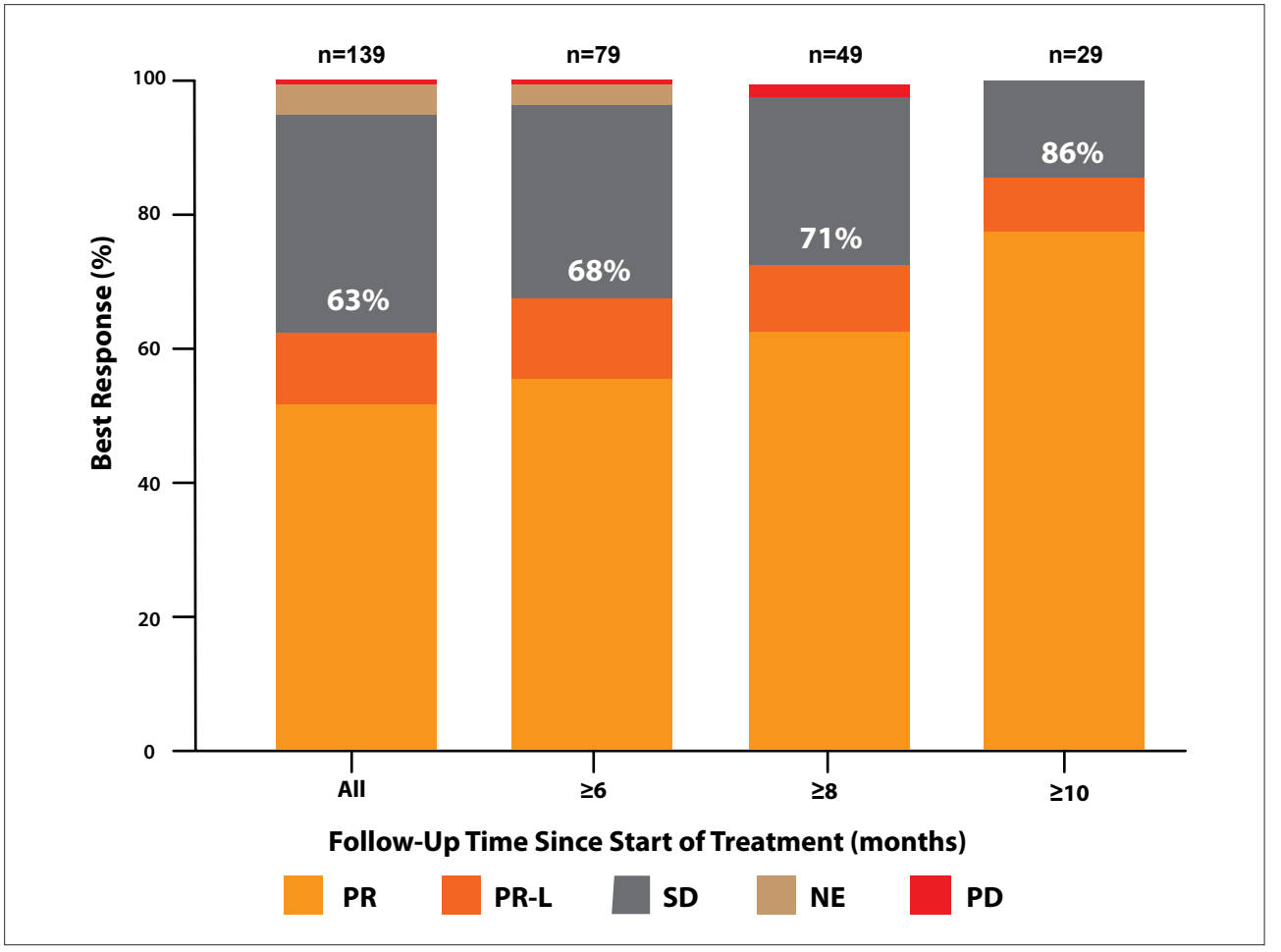

Figure 5. Overall response rates increased over time in the phase 1/2 BRUIN study of LOXO-305 in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. The analysis included patients who were evaluable for efficacy at the time of data cutoff. NE, not estimable; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD stable disease. Adapted from Mato A et al. ASH abstract 501. *Blood*. 2019;134(suppl 1).[9]

against both wild-type and *C481*-mutated BTK in cell and enzyme assays.[9,10] The phase 1/2 BRUIN study evaluated LOXO-305 in previously treated patients with advanced B-cell malignancies.[11] The phase 1 portion of the trial evaluated LOXO-305 dose escalation, using a 3+3 design. The LOXO-305 dose ranged from 25 mg daily to 300 mg daily. The safety population of the study included 170 CLL/SLL patients, with a median age of 69 years (range, 36-88 years). Patients had received a median of 3 prior treatments (range, 1-11), and 86% had received prior therapy with a BTK inhibitor. Among the latter group, 67% had discontinued prior BTK therapy owing to progressive disease, and 33% did so owing to toxicity or other reasons. At baseline, 27% of patients had a BTK *C481* mutation, and 4% had a *PLCG2* mutation. Molecular characteristics consistent with high-risk disease included unmutated *IGHV* in 88%, *TP53* mutation in 30%, 17p deletion (del[17p]) in 25%, and 11q deletion in 19%. Plasma exposure of LOXO-305 exceeded the BTK IC_{90} throughout the dosing interval at doses of 100 mg daily or higher, and plasma concentrations were dose-dependent and linear.

The ORR in 139 patients with CLL/SLL was 63%, including PRs in 50% and PRs with lymphocytosis in 14%. Among 121 patients who had received prior therapy with a BTK inhibitor, the ORR was 62%, including a PR rate of 47% and a PR with lymphocytosis rate of 15%. The ORR increased over time (Figure 5). After a median follow-up of 6 months (range, 0.6-17.8+ months), 94% of responding patients continued to show a response. Four patients discontinued treatment after disease progression, and 1 patient who achieved a PR discontinued therapy in order to undergo stem cell transplant. LOXO-305 yielded response rates of 50% or higher in patients with prior BTK exposure and in those with a *C481* mutation.

Among 323 patients treated at all dose levels of LOXO-305, the most common AEs of any grade were fatigue (20%) and diarrhea (17%). AEs of special interest were mostly grade 1/2 and included bruising (16%), rash (11%), arthralgia (5%), hemorrhage (5%), hypertension (5%), and atrial fibrillation/flutter (<1%). One patient (<1%) experienced grade 3 hemorrhage, and 4 patients (1%) developed grade 3 hypertension. No dose-limiting toxicities were reported, and the maximum tolerated dose was not reached. Five patients (1.5%) discontinued therapy owing to treatment-related AEs. The 200-mg daily dose of LOXO-305 was selected as the recommended phase 2 dose.

ABSTRACT SUMMARY Pooled Analysis of Cardiovascular Events From Clinical Trials Evaluating Acalabrutinib Monotherapy in Patients With Chronic Lymphocytic Leukemia

A retrospective study analyzed the incidence and types of cardiovascular AEs in CLL patients treated with acalabrutinib monotherapy in 4 clinical trials: ACE-CL-001, ACE-CL-007, ELEVATE-TN, and ACE-CL-309 (Abstract 3146). The study included 352 patients (46%) with treatment-naive CLL and 410 (54%) with relapsed or refractory disease. After a median follow-up of 25.9 months, 129 patients (17%) experienced a cardiac AE of any grade, with resulting discontinuation of acalabrutinib in 7 patients (0.9%). Four percent of patients treated with acalabrutinib monotherapy experienced atrial fibrillation. Cardiac events of grade 3 or higher occurred in 37 patients (5%), 18 of whom (49%) continued to receive acalabrutinib at data cutoff. Two grade 5 cardiac AEs occurred. The median time to onset of cardiac AEs was 10.1 months (range, 0.1-49.7 months).

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

The multicenter, randomized phase 3 ASCEND study compared acalabrutinib monotherapy vs standard of care in patients with relapsed or refractory CLL.[1,2] Prior to randomization, eligible patients were stratified by del(17p) status, ECOG performance status, and number of prior lines of therapy. Patients had received a median of 2 prior therapies (range, 1-10). Patients in the standard-of-care arm received the investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. Responses were evaluated by independent review based on iwCLL 2008 criteria, and the primary endpoint was PFS.[3] The trial assigned 154 patients to treatment with acalabrutinib. In the control arms, 118 patients received idelalisib plus rituximab and 35 received bendamustine plus rituximab. The median duration of treatment exposure was 21.9 months with acalabrutinib, 11.5 months with idelalisib plus rituximab, and 5.6 months with bendamustine plus rituximab. The relative dose intensity was at least 90% for all 3 regimens. The rate of treatment discontinuation was 27% in the acalabrutinib arm, 77% in the idelalisib arm, and 19% in the bendamustine arm.

In updated results based on a median of 22 months of follow-up, the estimated 18-month PFS was 82% with acalabrutinib vs 48% with the standard of care (HR, 0.27; 95% CI, 0.18-0.40; *P*<.0001), confirming previous reports. In the acalabrutinib arm, the median PFS was not reached (Figure 6). Acalabrutinib was superior to the other regimens in patients with del(17p) and *TP53* mutations (HR, 0.11; 95% CI, 0.04-0.34; Figure 7)

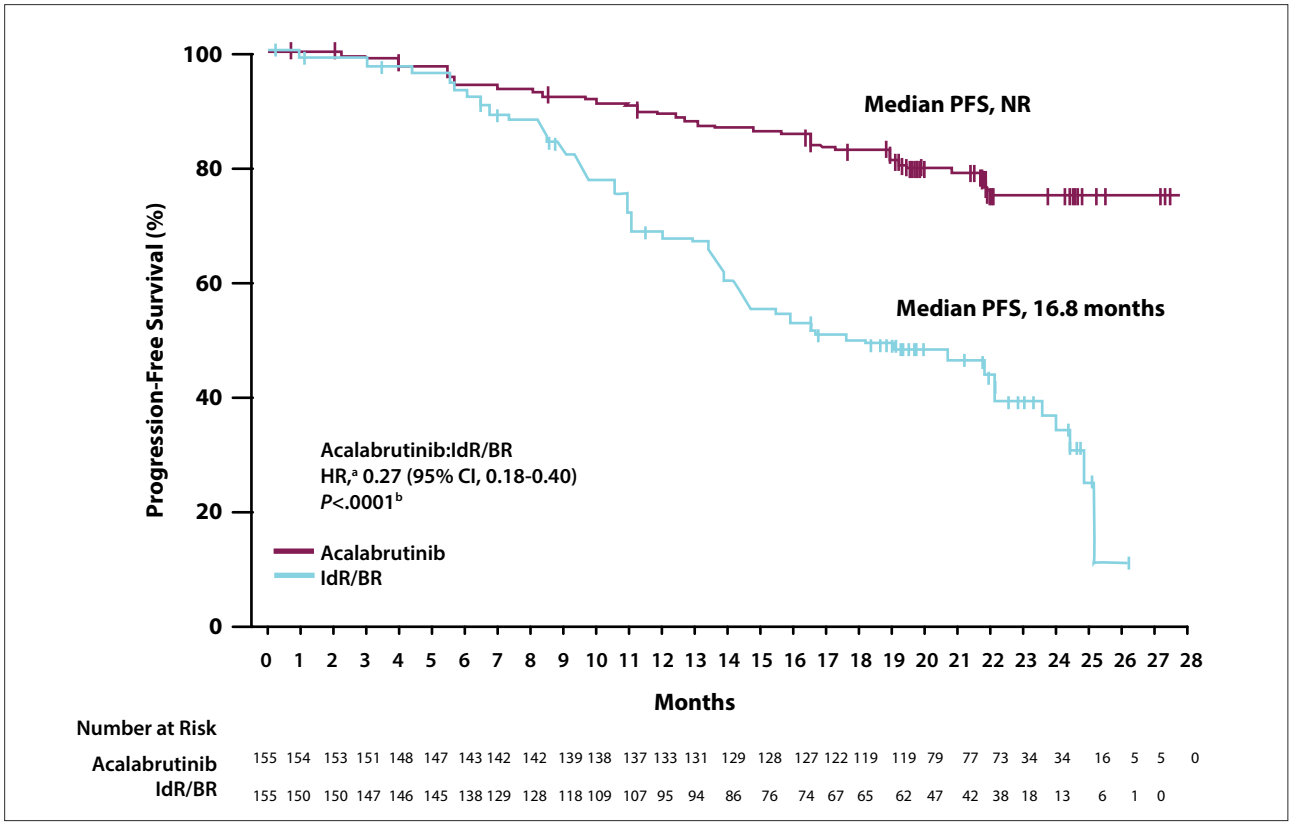

Figure 6. Progression-free survival among patients with relapsed or refractory chronic lymphocytic treated with acalabrutinib or the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in the phase 3 ASCEND trial. [a]The hazard ratio was based on a stratified Cox-Proportional-Hazards model, which was stratified by randomization stratification factors as recorded in an interactive voice/web response system. [b]The *P* value was based on a stratified log-rank test, which was stratified by randomization stratification factors as recorded in an interactive voice/web response system. BR, bendamustine plus rituximab; HR, hazard ratio; IdR, idelalisib plus rituximab; NR, not reached; PFS, progression-free survival. Adapted from Ghia P et al. ASH abstract 3140. *Blood.* 2020;136(suppl 1).[1]

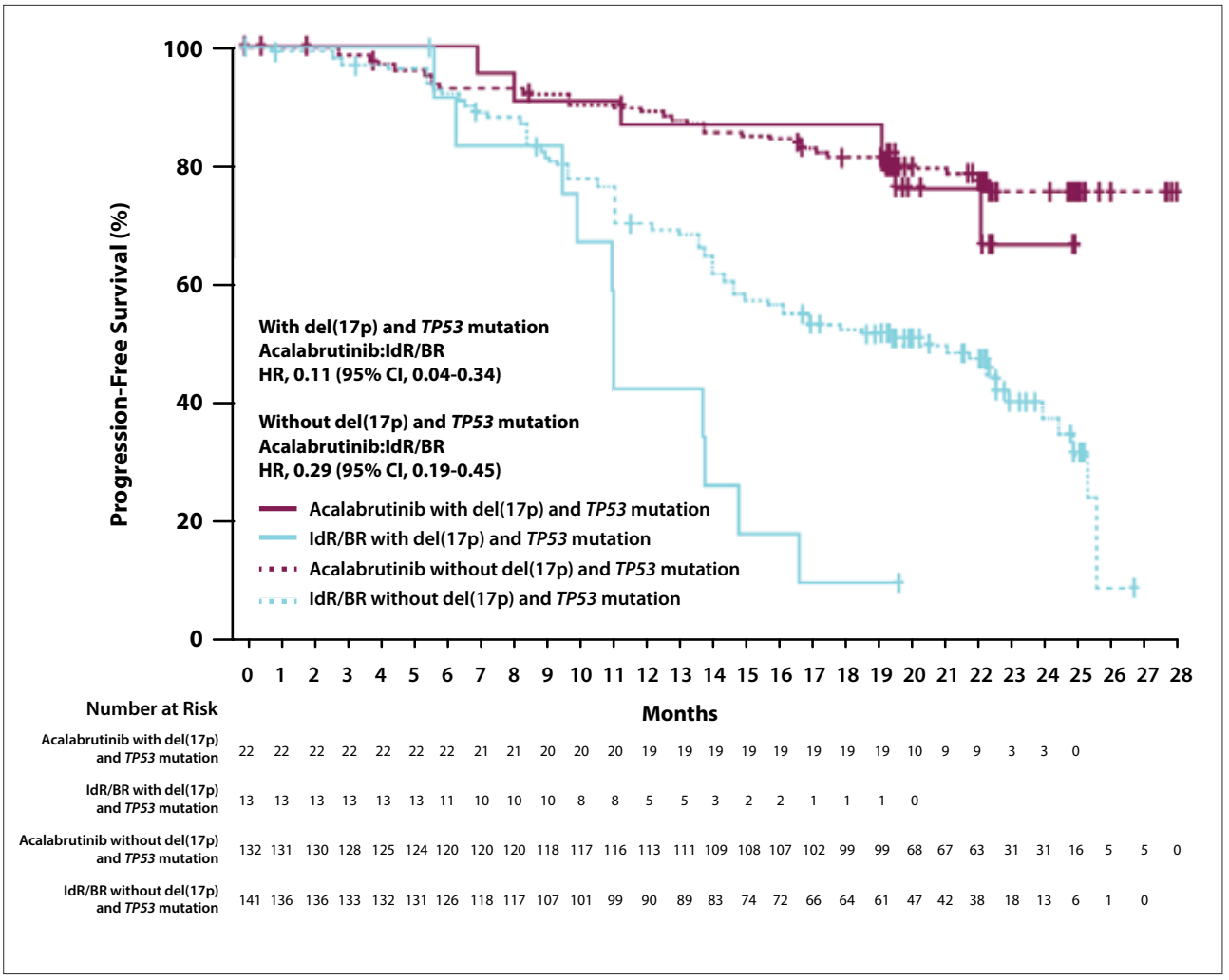

Figure 7. Progression-free survival according to genetic status among patients with relapsed or refractory chronic lymphocytic leukemia treated with acalabrutinib or the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in the phase 3 ASCEND trial. BR, bendamustine plus rituximab; del(17p), deletion 17p; HR, hazard ratio; IdR, idelalisib plus rituximab. Adapted from Ghia P et al. ASH abstract 3140. *Blood.* 2020;136(suppl 1).[1]

and in patients without these characteristics (HR, 0.29; 95% CI, 0.19-0.45). Acalabrutinib was also superior to the standard-of-care regimens in patients with unmutated *IGHV* (HR, 0.28; 95% CI, 0.18-0.43) or mutated *IGHV* (HR, 0.30; 95% CI, 0.12-0.76). The median overall survival was not reached. The median duration of response was superior with acalabrutinib (not reached vs 18 months; HR, 0.19; 95% CI, 0.11-0.33), as was the estimated 18-month duration of response rate (85.4% vs 49.4%).

The safety profile of acalabrutinib was similar to that of bendamustine plus rituximab and superior to that of the idelalisib combination in terms of AEs of grade 3 or higher (55% vs 90% with idelalisib/rituximab), serious AEs (33% vs 56%), and treatment-related AEs (70% vs 95%). AEs led to drug discontinuation in 14% of the acalabrutinib arm, 59% of the idelalisib arm, and 17% of the bendamustine arm. Grade 3 or higher AEs included infections (20% with acalabrutinib vs 25% in the control arm).

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Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 1-Year Disease-Free Survival Results From the MRD Cohort of the Phase 2 CAPTIVATE Study

The BTK inhibitor ibrutinib is associated with a significant improvement in overall survival as first-line treatment for CLL in phase 3 trials.[1,2] Venetoclax inhibits Bcl-2 and induces apoptosis in CLL cells, thus providing a complementary function to that of ibrutinib.[3]

The international, phase 2 CAPTIVATE study evaluated the combination of ibrutinib plus venetoclax as first-line therapy for CLL. The chemotherapy-free regimen was administered either as a fixed-duration treatment or a schedule based on MRD.[4] The study enrolled treatment-naive CLL patients with active disease who required treatment based on iwCLL 2008 criteria.[5] Patients were younger than 70 years and had an ECOG performance status of 0 or 1. All patients received 3 cycles of ibrutinib lead-in treatment followed by 12 cycles of ibrutinib plus venetoclax, at which point they were evaluated for MRD. Ibrutinib was administered at 420 mg daily, and the venetoclax dose was ramped up to 400 mg daily.

Patients with undetectable MRD that was not confirmed were randomly assigned to receive treatment with open-label ibrutinib monotherapy or ibrutinib plus venetoclax. Patients with confirmed undetectable MRD were randomly assigned to receive placebo or ibrutinib in a double-blind fashion. Undetectable MRD was defined as a malignant cell count in the peripheral blood and bone marrow below 10^{-4} as assessed by 8-color flow cytometry serially throughout 3 or more treatment cycles.

The primary endpoint was the 1-year rate of disease-free survival in patients with confirmed undetectable MRD after 12 cycles of combination therapy who were randomly assigned to placebo vs ibrutinib after induction therapy. Disease-free survival was defined as freedom from MRD relapse of more than 10^{-2} malignant cells, confirmed on 2 separate occasions, in the absence of disease progression or death.

The trial enrolled 164 patients. Their median age was 58 years (range, 28-69 years). Fifty-three patients (32%)

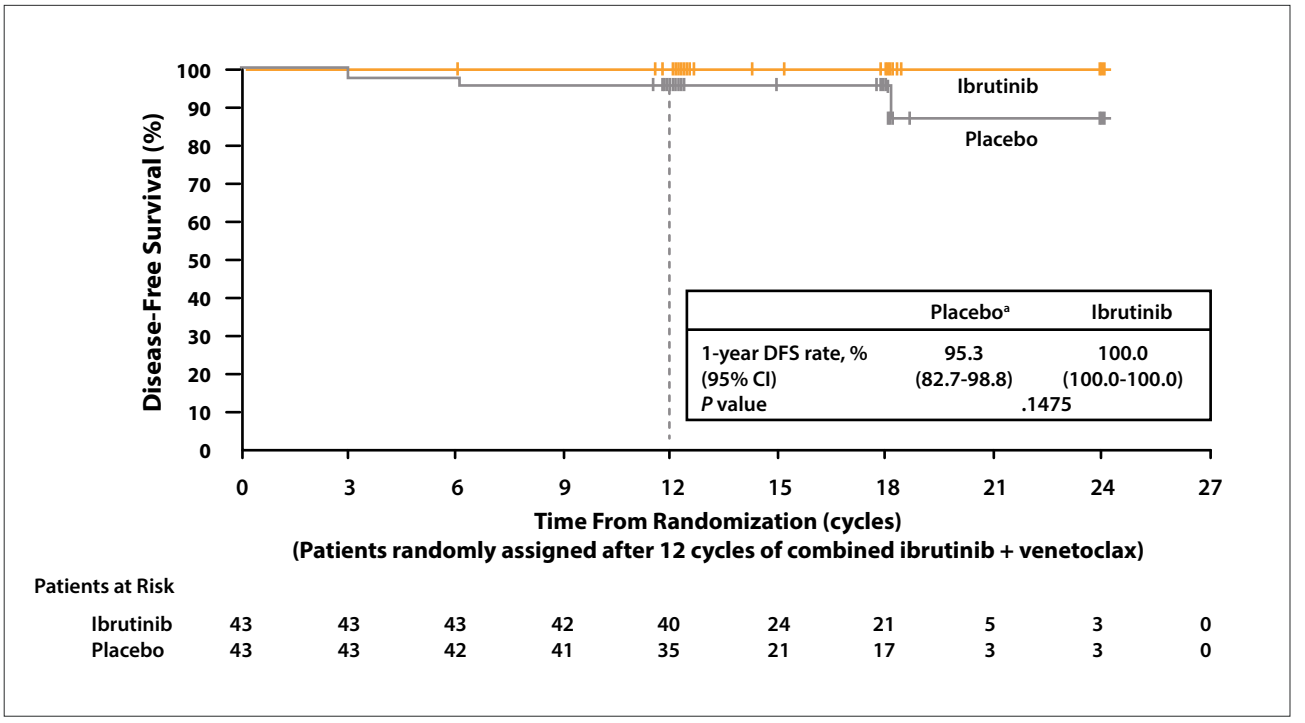

Figure 8. The rate of 1-year disease-free survival after randomization among patients with chronic lymphocytic leukemia/small lymphocytic lymphoma who had confirmed undetectable minimal residual disease in the phase 2 CAPTIVATE study. DFS, disease-free survival. [a]The 3 DFS events in the placebo arm were disease progression in 2 patients and MRD relapse in 1 patient. Adapted from Wierda WG et al. ASH abstract 123. *Blood.* 2020;136(suppl 1).[4]

had Rai stage III/IV disease, and 53 patients (32%) had a lymph node diameter of 5 cm or larger. High-risk features included unmutated *IGHV* in 60%, del(17p)/*TP53* mutation in 20%, complex karyotype in 19%, and del(11q) in 17%. A cytopenia was reported in 36% of patients, and 32% had an enlarged lymph node (≥5 cm). Administration of 3 cycles of ibrutinib lead-in therapy reduced the risk of tumor lysis syndrome and hospitalization.

After 12 cycles of ibrutinib plus venetoclax, the rate of undetectable MRD was 75% (95% CI, 69%-82%) in peripheral blood and 72% (95% CI, 65%-79%) in bone marrow. Among the patients who had matched peripheral blood and bone marrow samples at cycle 16, 93% had undetectable MRD in both sample types.

Among 164 patients in the entire study population, 149 were randomly assigned to treatment. Eighty-six of these patients (58%) achieved confirmed undetectable MRD. A trend toward an increased likelihood of having high-risk features was observed among patients who achieved confirmed undetectable MRD as compared with patients who did not. For example, unmutated *IGHV* was reported in 70% vs 46%, respectively, and del(11q) was reported in 21% vs 8%.

At a median follow-up of 16.6 months after randomization, the 1-year rate of disease-free survival was 100% with ibrutinib monotherapy vs 95.3% with placebo, a difference that did not reach statistical significance (*P*=.1475; Figure 8). At a median on-study follow-up of 31.3 months, the 30-month PFS was 95.3% for the 164 enrolled patients. The 30-month PFS rates were higher than 95% across all 4 randomized arms. Among the 63 patients with unconfirmed undetectable MRD, the rates of undetectable bone marrow MRD increased from 32% to 42% with ibrutinib alone and from 31% to 66% with ibrutinib plus venetoclax. Rates of undetectable MRD in peripheral blood remained at 45% with ibrutinib monotherapy and increased from 50% to 69% with further ibrutinib plus venetoclax. These increases in undetectable MRD were higher than those seen in patients with confirmed undetectable MRD prior to randomization.

Rates of AEs generally decreased after the first 6 months of combination therapy, regardless of subsequent therapy. AEs of grade 3 or higher were infrequent across all randomized arms. No new safety signals were observed.

ABSTRACT SUMMARY Five-Year Analysis of the MURANO Study Demonstrates Enduring Undetectable Minimal Residual Disease in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia Patients Following Fixed-Duration Venetoclax-Rituximab Therapy

Updated results from the phase 3 MURANO study continued to show a survival benefit with venetoclax plus rituximab vs bendamustine plus rituximab in patients with relapsed or refractory CLL (Abstract 125). This analysis provided data for a median follow-up of 59 months (range, 0-71.5). The median PFS was 53.6 months with the venetoclax combination vs 17.0 months with the bendamustine combination (HR, 0.19; 95% CI, 0.15-0.26; *P*<.0001). The 5-year overall survival was 82.1% with venetoclax vs 62.2% with bendamustine (HR, 0.40; 95% CI, 0.26-0.62; *P*<.0001). Undetectable MRD at the end of treatment with venetoclax plus rituximab was associated with improved outcomes. At 36 months, the rates of PFS since the end of treatment were 61.3% (95% CI, 47.3%-75.2%) among patients with undetectable MRD ($<10^{-4}$), 40.7% (95% CI, 19.2%-62.2%) among those with low MRD (10^{-4}-10^{-2}), and not evaluable among those with high MRD ($>10^{-2}$). The median time to MRD conversion in 83 patients was 19 months, and the median time from MRD conversion to disease progression was 25 months. The study investigators noted that a deep and durable response, plus favorable baseline characteristics, predicted sensitivity to retreatment. Unfavorable baseline characteristics were associated with faster MRD doubling rates. No new safety signals emerged.

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Umbralisib Plus Ublituximab (U2) Is Superior to Obinutuzumab Plus Chlorambucil (O+Chl) in Patients With Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: Results From the Phase 3 UNITY-CLL Study

Umbralisib is a dual inhibitor of phosphatidylinositol 3-kinase delta (PI3Kδ) and casein kinase-1ε.[1] With high selectivity for the δ form of PI3K, umbralisib is associated with low rates of immune-mediated toxicity and treatment discontinuation owing to AEs. Ublituximab is a novel anti-CD20 antibody that targets a unique epitope on CD20.[2] This antibody was glycoengineered to enhance antibody-dependent cellular cytotoxicity. The randomized phase 3 UNITY-CLL study compared the combination of umbralisib and ublituximab (U2) vs obinutuzumab and chlorambucil among patients with CLL.[3] Enrolled patients had treatment-naive or previously treated CLL that required treatment based on iwCLL criteria, as well as an ECOG performance status of 0 to 2 and adequate organ function. Patients were stratified for randomization based on del(17p) status and receipt of prior treatment. Patients were initially randomly assigned into 4 treatment arms to receive U2, obinutuzumab and chlorambucil, umbralisib monotherapy, or ublituximab monotherapy.

After the contribution of the single agents to the U2 combination was established, the 2 monotherapy arms were closed, and additional patients were randomly assigned into the U2 arm and the obinutuzumab/chlorambucil arm. Each treatment cycle was 28 days. Umbralisib (800 mg) was administered once daily. Ublituximab (900 mg) was administered with a split dose on days 1 and 2, followed by the full dose on days 8 and 15 of cycle 1, day 1 of cycles 2 to 6, and on day 1 every 3 cycles after cycle 6. Obinutuzumab (1000 mg) was administered with a split dose on days 1 and 2, followed by the full dose on days 8 and 15 of cycle 1 and on day 1 of cycles 2 to 6. Chlorambucil (0.5 mg/kg) was administered on days 1 and 15 of cycles 1 to 6. The primary endpoint was PFS for U2 vs obinutuzumab and chlorambucil based on independent review.

The study randomly assigned 421 patients to treatment with U2 or obinutuzumab plus chlorambucil.

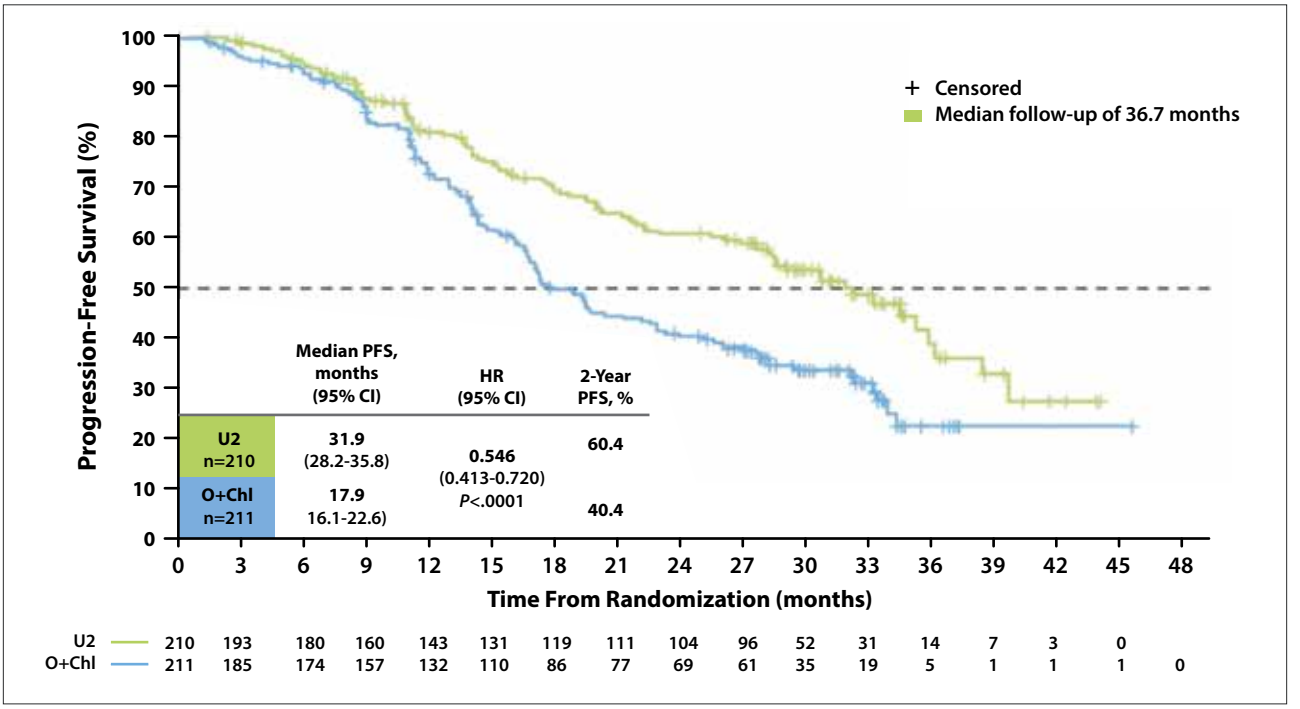

Figure 9. Progression-free survival among patients with chronic lymphocytic leukemia treated with umbralisib plus ublituximab or obinutuzumab plus chlorambucil in the phase 3 UNITY-CLL study. HR, hazard ratio; O+Chl, obinutuzumab plus chlorambucil; PFS, progression-free survival; U2, umbralisib plus ublituximab. Adapted from Gribben J et al. ASH abstract 543. *Blood.* 2020;136(suppl 1).[3]

The baseline characteristics were well balanced between the 2 arms. The patients' median age was 67 years (range, 36-91 years). Fifty-seven percent of patients were treatment-naive. High-risk genomic features included unmutated *IGHV* in 56%, del(11q) in 20%, and del(17p) in 10%.

The median treatment exposure was 21.1 months (range, 0.03-46.3 months) for ublituximab, 20.5 months (range, 0.03-47.2 months) for umbralisib, 4.7 months (range, 0.03-7.4 months) for obinutuzumab, and 5.1 months (range, 0.03-7.4 months) for chlorambucil. After a median follow-up of 36.7 months, the median PFS was 31.9 months (95% CI, 28.2-35.8 months) in the U2 arm vs 17.9 months (95% CI, 16.1-22.6 months) in the control arm (HR, 0.546; 95% CI, 0.413-0.720; *P*<.0001; Figure 9). The estimated 2-year PFS rates were 60.8 months vs 40.4 months, respectively. The median PFS in previously treated patients was 19.5 months with the U2 regimen vs 12.9 months with the control (HR, 0.601; 95% CI, 0.415-0.869; *P*<.01). The estimated 2-year PFS rates were 41.3% vs 24.8%, respectively.

The ORR was 83.3% with U2 vs 68.7% with obinutuzumab plus chlorambucil (*P*<.001; Figure 10). Most subgroups benefited from U2 compared with obinutuzumab plus chlorambucil. U2 yielded a superior ORR in treatment-naive patients (84% vs 78%), previously treated patients (82% vs 57%), and those with prior exposure to a BTK inhibitor (57% vs 25%). Durable responses were observed, with 62% of patients maintaining their response at 2 years.

Serious AEs were observed in 46.1% of the U2 arm vs 23.5% of the control arm. AEs of grade 3 or higher were observed in 82.0% vs 66.0%, respectively, and grade 5 AEs occurred in 3.9% vs 2.5%. More patients in the U2 arm discontinued study treatment owing to an AE (16.5% vs 7.6%). The most common grade 3/4 AEs in the U2 arm were neutropenia (31%) and diarrhea (12%, all grade 3), followed by infusion-related reactions (1.9%) and fatigue (1.9%). In the U2 arm, the most common grade 3 or higher AEs of clinical interest were alanine transaminase elevation (8.5%), opportunistic infections (5.8%), and aspartate transaminase elevation (5.3%).

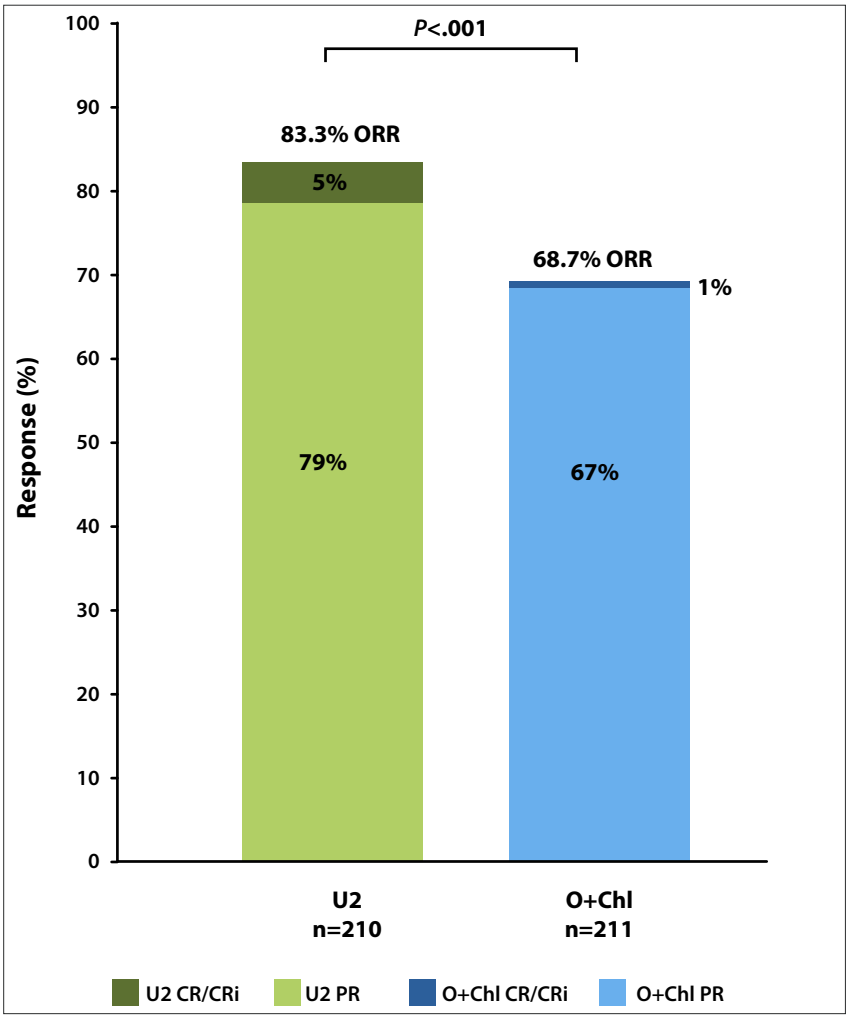

Figure 10. Response rates among patients with chronic lymphocytic leukemia treated with umbralisib plus ublituximab or obinutuzumab plus chlorambucil in the phase 3 UNITY-CLL study. CR, complete response; CRi, complete response with incomplete hematologic recovery; HR, hazard ratio; O+Chl, obinutuzumab plus chlorambucil; ORR, overall response rate; PR, partial response; PFS, progression-free survival; U2, umbralisib plus ublituximab. Adapted from Gribben J et al. ASH abstract 543. *Blood.* 2020;136(suppl 1).[3]

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TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel in Combination With Ibrutinib for Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Lisocabtagene maraleucel is an autologous chimeric antigen receptor (CAR) T-cell therapy directed at CD19.[1] The T-cell product is administered by delivering equal doses of engineered CD8-positive and CD4-positive T cells. The TRANSCEND CLL 004 study evaluated lisocabtagene maraleucel in patients with relapsed or refractory CLL/SLL.[2-4] Enrolled patients were ineligible for treatment with a BTK inhibitor or had not responded to previous treatment. The trial enrolled patients with high-risk disease who had an inadequate response to 2 or more prior therapies and patients with standard-risk disease who had an inadequate response to at least 3 prior therapies. Bridging therapy was allowed. The phase 1 portion of the trial investigated 2 dose levels of CAR T-cell therapy: 50×10^6 CAR-positive T cells and 100×10^6 CAR-positive T cells. Dose-limiting toxicities were evaluated for 28 days after the lisocabtagene maraleucel infusion, and responses were assessed based on iwCLL 2018 criteria.[5]

Twenty-three patients in the trial received lisocabtagene maraleucel monotherapy.[3] The patients' median age was 66 years (range, 50-80 years), and the median time since diagnosis was 87.5 months (range, 30-209 months). Eight patients (35%) had bulky disease. Fifteen patients (65%) had Rai stage III/IV disease, and 19 (83%) had a high-risk genetic feature. Patients had received a median of 4 prior lines of therapy (range, 2-11). Two dose-limiting toxicities were reported at the higher dose level of lisocabtagene maraleucel therapy. Common grade 3/4 treatment-emergent AEs included anemia, thrombocytopenia, and neutropenia, observed in 70% to 74% of patients, and leukopenia in 43%. Cytokine release syndrome of any grade was observed in 74% of patients, including 2 patients (9%) with grade 3 cases. Neurologic events of any grade were observed in 9 patients (39%), with neurologic AEs of grade 3 or higher observed in 5 patients (22%).

After a median follow-up of 24 months, the ORR was 82%, including a CR/CRi rate of 46%. Six patients (27%) experienced a deepening of response. Fifty percent of patients (11/22) continued to demonstrate a response at 12 months, and 2 of these patients progressed after 12 months. Among 15 patients with a CR or PR and undetectable MRD in the peripheral blood, 4 patients had progressed, including 3 owing to Richter transformation. The median duration of response was not reached (95% CI, 4.8 months to not reached; Figure 11), and the median PFS was 18 months (95% CI, 3.0 months to not reached). In the subgroup of 11 patients who had previously progressed on a BTK inhibitor and venetoclax, the median duration of response was 17 months (95% CI, 1.9 months to not reached), and the median PFS was 13 months (95% CI, 2.8 months to not reached). The lisocabtagene maraleucel product was detected in 50% of patients (6/12) at 12 months and in 18% of patients (2/11) at 18 months.

The TRANSCEND NHL 004 study contained a second arm in which 19 patients with relapsed or refractory CLL received the lisocabtagene maraleucel transfusion (at either dose level) plus ibrutinib (420 mg daily). These patients had a median age of

ABSTRACT SUMMARY Adverse Events in Clinical Trials of Ibrutinib and Acalabrutinib for B-Cell Lymphoproliferative Disorders: A Systematic Review and Network Meta-Analysis

The first-generation BTK inhibitor ibrutinib has been associated with an increased risk of cardiovascular events. Acalabrutinib is a second-generation BTK inhibitor with fewer off-target effects than ibrutinib. No head-to-head comparisons of ibrutinib and acalabrutinib have been conducted. A systemic review and meta-analysis analyzed the reported AEs in 27 prospective clinical trials (Abstract 1317). These trials included data for 3207 patients. The most common AEs reported with ibrutinib were diarrhea, occurring in 46% of patients; and myalgias/arthralgias, occurring in 37%. For acalabrutinib, the most common AEs were headache, reported in 37%; diarrhea, occurring in 30%; and peripheral edema, occurring in 21%. The most common any-grade cardiovascular AEs with ibrutinib were bleeding/bruising (reported in 32%), hypertension (23%), and atrial fibrillation (9%). With acalabrutinib, the most common any-grade cardiovascular AEs were bleeding/bruising (41%) and hypertension (6%). The investigators concluded that acalabrutinib appeared to have an overall improved safety profile compared with ibrutinib. In particular, improvements were seen in rates of anemia, thrombocytopenia, and cardiovascular AEs, including atrial fibrillation and hypertension.

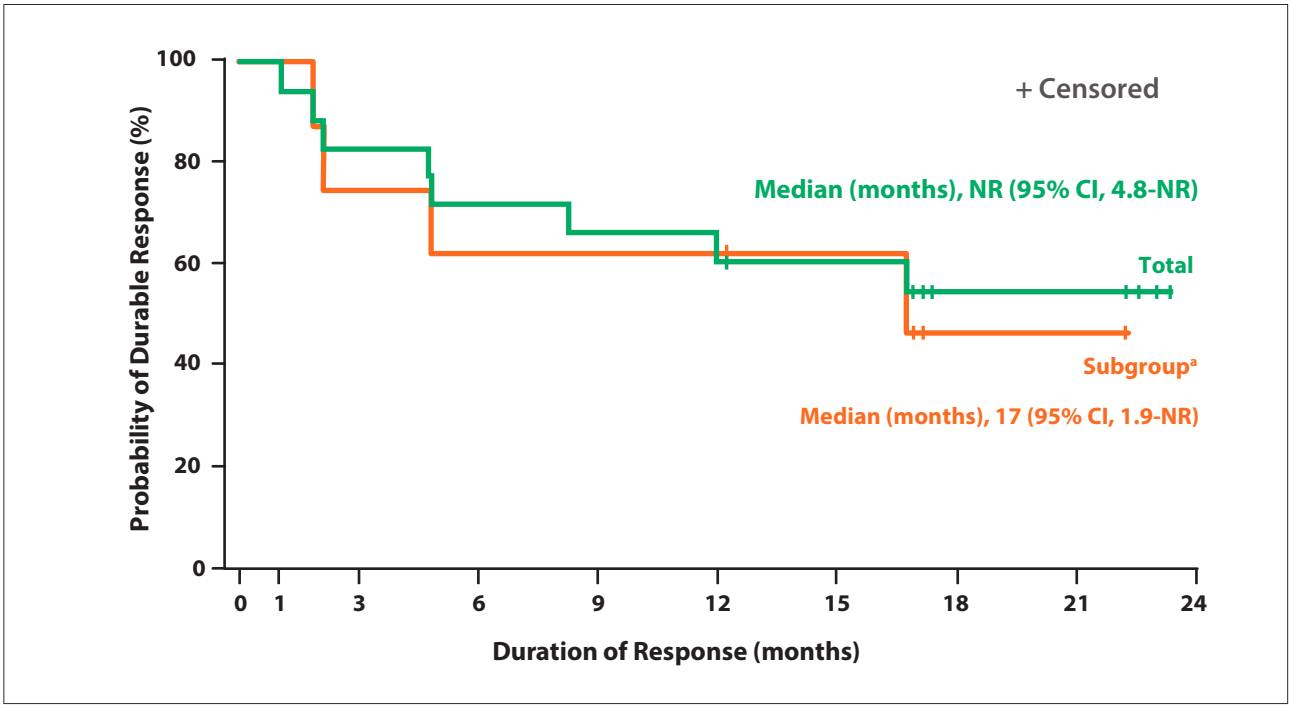

Figure 11. Probability of a durable response among patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma who received lisocabtagene maraleucel in the phase 1 cohort of the TRANSCEND CLL 004 trial. [a]Defined as patients whose disease progressed during treatment with a Bruton tyrosine inhibitor and who had an inadequate response to venetoclax owing to progression, intolerance, or failure to respond after at least 3 months of therapy. NR, not reached. Adapted from Siddiqi T et al. ASH abstract 546. *Blood.* 2020;136(suppl 1).[3]

61 years (range, 50-77 years), with a median time since diagnosis of 121 months (range, 21-252 months). Forty-seven percent of patients had Rai stage III/IV disease. Ninety-five percent had a high-risk feature, such as complex karyotype in 42%, del(17p) in 42%, and mutated *TP53* in 32%. The median number of prior lines of therapy was 4 (range, 1-10). Common grade 3/4 treatment-emergent AEs included neutropenia (89%), anemia (47%), and febrile neutropenia (26%). Fourteen patients (74%) experienced any-grade cytokine release syndrome, including 1 patient (5%) with grade 3 cytokine release syndrome. Neurologic events of any grade were observed in 6 patients (32%), including 3 patients with grade 3 events (16%). Ibrutinib therapy was discontinued owing to an AE in 4 patients (21%). After 10 months of follow-up, the ORR was 95% (18/19), including a CR/CRi rate of 63%. Eighty-nine percent of patients (11/19) achieved undetectable MRD, with 1 patient later progressing owing to Richter transformation. The lisocabtagene maraleucel product was detected in 38% of patients (6/16) at 6 months and in 20% of patients (1/5) at 12 months.

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Continued Long-Term Responses to Ibrutinib + Venetoclax Treatment for Relapsed/Refractory CLL in the Blood Cancer UK TAP CLARITY Trial

The phase 2 Blood Cancer UK TAP CLARITY trial evaluated the combination of ibrutinib plus venetoclax among patients with relapsed or refractory CLL.[1,2] The trial design incorporated a plan to stop therapy early if undetectable MRD (<0.01%) was achieved in the peripheral blood and bone marrow. After 2 months of treatment with ibrutinib monotherapy, venetoclax was added first at a daily dose of 10 mg or 20 mg, then escalated weekly to a final daily dose of 400 mg. Paired samples of peripheral blood and bone marrow were evaluated at months 8, 14, and 26. Longitudinal samples of peripheral blood were obtained at multiple time points. An updated analysis provided data regarding long-term responses.[2]

The trial enrolled 54 patients. Most patients (69%) were male, and their median age was 64 years. Their median number of prior therapies was 1 (range, 1-6). Bulky lymph nodes (≥5 cm) were reported in 8%. High-risk genetic factors included del(17p) in 20%, del(11q) in 25%, and unmutated *IGHV* in 75%. During the first 8 weeks of ibrutinib monotherapy, 4 patients discontinued treatment after developing treatment-related adverse events. The trial recruited 50 patients to the combination portion, and all were successfully treated through the venetoclax dose-escalation phase.

Therapy was halted after confirmation of a CR based on iwCLL 2008 criteria and MRD reduction to below 10^{-4} CLL cells in the peripheral blood and bone marrow (MRD4). Among patients with MRD4 at month 8, treatment with ibrutinib and venetoclax was stopped at month 14. Among those with MRD4 at month 14 and/or month 26, ibrutinib and venetoclax were stopped at month 26. When MRD was detectable at month 26, venetoclax was stopped, but ibrutinib was continued until disease progression or toxicity. The trial protocol was amended to permit patients without an MRD4 at month 26 to receive 12 months of venetoclax in addition to ibrutinib.

The primary endpoint was MRD4 (<0.01%) in the bone marrow after 12 months of treatment with ibrutinib plus venetoclax. At month 14, 58% of patients were MRD-negative in the peripheral blood and 40% of patients were MRD-negative in the bone marrow. Levels of trephine were normal in 81%. Among patients who had relapsed after treatment with FCR or bendamustine plus rituximab, 70% were MRD-negative in the peripheral blood and 45% were MRD-negative in the bone marrow. These rates were 67% and 56%, respectively, among patients who had received previous treatment with idelalisib. The ORR was 100% at month 8, 98% at month 14, 92% at month 26, and 90% at month 38. The rates of CR were 40%, 50%, 64%, and 68%, respectively. Among patients receiving at least 1 treatment at the time of assessment, the ORR was 94% at month 25 and 85% at month 38, with CR rates of 59% and 65%, respectively. At month 38, rates of MRD4 negativity were 50% in the peripheral blood and 40% in the bone marrow among all evaluable patients. Responses correlated with the initial depletion rate. After treatment, a sustained MRD of less than 0.01% was reported in 68% of patients with higher levels of depletion vs 20% among those with lower levels of depletion. The median PFS and overall survival were not reached. At month 36, the estimated rate of PFS was 95.9%, and the estimated rate of overall survival was 97.7%.

There were 6 cases of atrial fibrillation/flutter occurring in 5 patients. Three events were grade 1/2, and the other 3 were grade 3. No grade 4 events were reported. Any-grade febrile neutropenia occurred in 2 patients. There were 37 reports of a decrease in neutrophil count (occurring in 13 patients). Most events (24) were grade 3. There was a single case of tumor lysis syndrome, which occurred with the 200-mg dose of venetoclax. This case was managed by delaying treatment. The protocol included a recommendation to administer granulocyte colony–stimulating factor to maintain the neutrophil count above 1×10^9/L.

In conclusion, at a follow-up of 38 months, the response to ibrutinib plus venetoclax was sustained, despite planned treatment discontinuation among patients with MRD-negative disease. No new safety signals arose in this long-term follow-up analysis. Two patients had COVID-19 infection, and both recovered. The investigators found that the initial rate of disease depletion achieved during the first 2 months of treatment with ibrutinib plus venetoclax was highly predictive of longer-term response. Patients without rapid disease clearance who had persistent MRD after 12 months of combination treatment tended to have stable or slowly decreasing levels of disease similar to those reported with ibrutinib monotherapy.

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Highlights in Chronic Lymphocytic Leukemia From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

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Several studies presented at the 62nd American Society of Hematology Annual (ASH) Meeting and Exposition provided insight into the management of patients with chronic lymphocytic leukemia (CLL). Some of the highlights to me were data presented on treatments such as the triplet regimens of BTK inhibitors with venetoclax and obinutuzumab; the doublet regimen of ibrutinib and venetoclax; LOXO-305; umbralisib plus ublituximab; and lisocabtagene maraleucel.

My colleagues and I presented the results of a phase 2 trial of acalabrutinib, venetoclax, and obinutuzumab (AVO) for the frontline treatment of patients with CLL.[1] An interesting aspect of the study is that the population was enriched for high-risk patients with *TP53*-aberrant CLL; 38.6% of patients had deletion 17p or the *TP53* mutation. The study showed very deep responses in terms of minimal residual disease (MRD). For example, the rate of undetectable bone marrow MRD was 76.5% on day 1 of cycle 16. The benefit was similar in patients with high-risk disease vs standard-risk, as this rate was 70.0% among patients with *TP53*-aberrant disease. Another notable aspect of the AVO study is the favorable safety profile. Although the regimen consisted of 3 drugs, the rates of severe cytopenias, atrial fibrillation, and infection were low. Grade 3 or higher infection, atrial fibrillation, and infusion-related reactions were reported in 2% of patients each. No major bleeding issues occurred. The study explored the use of a shorter 4-week venetoclax dose ramp-up instead of the usual 5 weeks. This more convenient dosing strategy was enabled by the effective reduction in disease burden among patients who received acalabrutinib and obinutuzumab. There were no reports of tumor lysis syndrome associated with starting venetoclax.

Dr William Wierda presented results from the MRD cohort of the phase 2 CAPTIVATE trial, an important study of the doublet regimen of ibrutinib and venetoclax in the frontline setting.[2] According to the study design, patients could be randomly assigned to additional therapy after separation into cohorts with or without confirmed undetectable MRD. Overall, this early report suggested that ibrutinib and venetoclax was an effective combination in the frontline setting. The rate of undetectable MRD in the bone marrow was 72% among evaluable patients. At this point in the analysis, among patients with confirmed undetectable MRD who completed the initial 15 months of therapy, similar rates of disease-free survival at 1 year were reported in patients who received an additional year of ibrutinib vs placebo (100.0% vs 95.3%, respectively; P=.1475). It is reassuring that 1 year of treatment with ibrutinib plus venetoclax provided good durability, and this observation raises the prospect that such patients may do well without the need for continuous BTK inhibitor therapy. However, longer follow-up and phase 3 data are needed before the results with this regimen can be considered practice-changing.

Dr Anthony Mato provided an updated analysis of a study of LOXO-305 in patients with CLL or small lymphocytic leukemia (SLL).[3] Early data presented at the previous ASH meeting suggested that LOXO-305 might be a well-tolerated, highly effective Bruton tyrosine kinase (BTK) inhibitor, even for patients with the BTK *C481* mutation.[4] The updated data confirmed the previous results, but in much larger patient numbers. It is clear that LOXO-305 is an active drug for patients with both mutated and wild-type *BTK*. The overall response rate was 63%. Patients who had progressed on ibrutinib and venetoclax still responded to LOXO-305. This agent appears to have a safe toxicity profile, with no significant rates of atrial fibrillation or bleeding, which are typically seen with BTK inhibitors. These exciting early data will inform the design of phase 3 registrational trials to gain approval in CLL from the US Food and Drug Administration.

Dr John G. Gribben presented results from the phase 3 UNITY-CLL study, which compared umbralisib plus ublituximab (also known as U2)

vs obinutuzumab plus chlorambucil in patients with CLL.[5] Results from this registrational study are likely to lead to FDA approval of umbralisib and ublituximab, which would be the first approval for each of these drugs. This study provided helpful data regarding the safety and efficacy profile for the U2 regimen. The median progression-free survival was 31.9 months with the U2 regimen vs 17.9 months with obinutuzumab/chlorambucil (*P*<.0001). Although obinutuzumab/chlorambucil was not the strongest comparator regimen, it was useful because it has recently been the control arm in several other studies, such as the CLL14 trial.[6] Another study expected to read out soon is the GLOW trial, which is comparing ibrutinib plus venetoclax to obinutuzumab plus chlorambucil.[7] Results are not yet available, but the common comparator arm in these studies should facilitate cross-study comparison. Results from the UNITY CLL study suggest that umbralisib is fairly well-tolerated, with a differentiated safety profile compared with other phosphatidylinositol 3 (PI3)-kinase inhibitors.[5] For example, this study is the first to provide evidence that it is feasible from a safety perspective to use a PI3 kinase inhibitor for the frontline treatment of CLL. The combination of umbralisib plus ublituximab will have a role in the CLL treatment paradigm. This regimen may not necessarily displace BTK inhibitors or venetoclax-based therapy for the majority of patients, but it will provide an alternative for some patients, particularly those who have cardiovascular comorbidities or who may have difficulties with venetoclax dose ramp-up.

Two presentations provided analyses from the phase 1 TRANSCEND CLL 004 trial of lisocabtagene maraleucel, with or without ibrutinib, in patients with relapsed or refractory CLL or SLL.[8,9] Dr Tanya Siddiqi provided an update of the data for lisocabtagene maraleucel monotherapy.[8] At a median follow-up of 24 months, lisocabtagene maraleucel appeared to be active, even in patients with very high-risk CLL, including those who had progressed during treatment with ibrutinib and venetoclax. The rate of complete response with or without complete blood count recovery was 46%. Dr William Wierda presented new data for the cohort treated with ibrutinib plus lisocabtagene maraleucel.[9] The rate of complete response with or without complete blood count recovery was 63%, and the rate of undetectable MRD in the bone marrow was 79%. These responses are notable in this heavily pretreated group of patients, although longer follow-up is needed to understand more about the durability of these responses. The combination of lisocabtagene maraleucel plus ibrutinib appeared to be tolerable from a safety perspective, with a similar or possibly even slightly better adverse event profile as lisocabtagene maraleucel alone. Clinicians who treat patients with CLL are curious about whether these strategies can be used to manipulate the immune system to enhance the activity of CAR T cells. This study is among the first to provide proof of principle that it may be possible.

Dr Arnon Kater presented a 5-year follow-up analysis of the MURANO study.[10] This data set is important because the MURANO trial established venetoclax plus rituximab as a standard of care for patients with relapsed/refractory CLL. This update provided the first data for the median progression-free survival, which was 53.6 months for venetoclax plus rituximab vs 17.0 months for bendamustine plus rituximab (*P*<.0001). It is helpful to remember this duration as we counsel patients about what they are likely to expect during treatment with venetoclax plus rituximab. These data are promising because they suggest that with 2 years of treatment, the majority of patients can obtain a remission lasting at least 2 additional years while off all treatment. Data presented at the ASH meeting by Dr Rosemary Harrup and colleagues suggest that it is possible to successfully re-treat any of these patients with venetoclax, and that BTK inhibitors could be used after venetoclax-based therapy with good effect.[11] This updated analysis of the MURANO study provides strong support for the utility of the venetoclax/rituximab regimen in patients with relapsed CLL.

This analysis also provided interesting data on the clonal dynamics of MRD recurrence among patients enrolled in the MURANO trial.[10] This information is helpful when considering the patients who are more likely to quickly develop recurrent disease after completing therapy. The analysis showed that patients with 17p deletion, unmutated *IGHV*, or genomic complexity all seemed to have faster regrowth of disease after completion of therapy. This observation could help guide the approach to disease monitoring after therapy and predict when patients may need to initiate treatment again. The investigators carefully documented the median time to MRD recurrence, as well as the median time from MRD recurrence to clinical disease progression. These markers can provide insight as we counsel patients about their likely length of remission, and when additional treatment might be needed.

Dr Othman Al-Sawaf provided an updated analysis of the CLL14 trial, the study of time-limited venetoclax/obinutuzumab as frontline treatment for CLL.[12] The analysis evaluated the clonal dynamics of patients treated with venetoclax during the study, with a focus on how the level of clones can evolve over time in patients with or without undetectable MRD. A current question in the field is whether 1 year is the optimal treatment duration for venetoclax plus obinutuzumab. This analysis compared the MRD change from halfway through the year of therapy vs after the year of therapy

was completed. Among the patients who still had detectable MRD at the end of treatment, approximately half had increasing MRD during treatment with venetoclax. It might be expected that additional venetoclax would not be helpful in this group of patients. In contrast, in half the group, MRD decreased during the second 6-month period of treatment with venetoclax. This finding suggests that additional venetoclax therapy might be helpful for these patients. These results are not practice-changing but more hypothesis-generating, and should inspire a trial designed to determine the length of therapy based not only on single MRD tests, but also on serial MRD testing, to identify patterns of change over time.

This analysis of the CLL14 study also generated updated data regarding survival for patients treated with this 1-year venetoclax/obinutuzumab regimen. At 4 years, 74% of the patients were progression-free. The previous data set had reported a progression-free survival rate of 82% at 3 years.[6] Therefore, only approximately 8% of patients developed progressive disease with an additional year of follow-up, and that was in patients who were off all therapy. These data reinforce the durability of response after 1 year of treatment with venetoclax plus obinutuzumab, particularly for those patients with mutated *IGHV* and other types of lower-risk disease. The report did not provide data comparing progression-free survival among patients with or without mutated *IGHV*, but this analysis is eagerly awaited.

Disclosure

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