

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in Chronic Lymphocytic Leukemia From the 2019 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2019 ASCO Annual Meeting

• May 31-June 4, 2019 • Chicago, Illinois

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**Special Reporting on:**

- Final Analysis From RESONATE: Six-Year Follow-Up in Patients With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma on Ibrutinib
- Acalabrutinib With Obinutuzumab in Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: Three-Year Follow-Up
- Long-Term Follow-Up of Previously Untreated Patients With Chronic Lymphocytic Leukemia Treated With Ofatumumab and Chlorambucil: Final Analysis of the Phase 3 COMPLEMENT 1 Trial
- TRANSCEND CLL 004: Minimal Residual Disease Negative Responses After Lisocabtagene Maraleucel (JCAR017), a CD19-Directed CAR T-Cell Product, in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
- Phase 1/2 Trial of Cirmtuzumab and Ibrutinib: Planned Analysis of Phase 1 CLL Cohorts
- Effect of Fixed-Duration Venetoclax Plus Obinutuzumab on Progression-Free Survival, and Rates and Duration of Minimal Residual Disease Negativity in Previously Untreated Patients With Chronic Lymphocytic Leukemia and Comorbidities
- Effect of Dose Modifications on Response to Duvelisib in Patients With Relapsed/Refractory CLL/SLL in the DUO Trial
- Phase 2 Study of Acalabrutinib in Ibrutinib-Intolerant Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia
- Outcomes in Chronic Lymphocytic Leukemia Patients With *NOTCH1* Signaling Pathway Mutations

**PLUS Meeting Abstract Summaries**

**With Expert Commentary by:**

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# A National Comprehensive Cancer Network® (NCCN®) Recommendation

## **IBRUTINIB (IMBRUVICA®) IS THE ONLY NCCN CATEGORY 1 PREFERRED REGIMEN IN FIRST-LINE CLL/SLL\***

\*As monotherapy for CLL/SLL without del 17p/TP53 mutation.

**Category 1:** Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Preferred intervention:** Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

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### **INDICATIONS**

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of patients with:

- Chronic lymphocytic leukemia (CLL)/ Small lymphocytic lymphoma (SLL)
- CLL/SLL with 17p deletion

### **IMPORTANT SAFETY INFORMATION**

#### **WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

**Please see additional Important Safety Information and Brief Summary on the following pages.**

  
**imbruvica®**  
(ibrutinib)  
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

# IBRUTINIB (IMBRUVICA®) Is the **Only** NCCN Category 1 Preferred Regimen\*

\*As monotherapy for CLL/SLL without del 17p/TP53 mutation.

Suggested treatment regimens for first-line therapy in CLL/SLL without del 17p/TP53 mutation		
	Preferred regimens	Other recommended regimens <sup>†</sup> (alphabetical by category)
Frail patients with significant comorbidity OR age ≥65 years and younger patients with significant comorbidities	<b>Ibrutinib (IMBRUVICA®) (category 1)</b>  Venetoclax + obinutuzumab (category 2A)	<ul style="list-style-type: none"> <li>• Bendamustine + an anti-CD20 monoclonal antibody<sup>‡</sup> (category 2A)</li> <li>• Chlorambucil + an anti-CD20 monoclonal antibody (category 2A)</li> <li>• High-dose methylprednisolone (HDMP) + rituximab (category 2B)</li> <li>• Ibrutinib + obinutuzumab (category 2B)</li> <li>• Obinutuzumab (category 2B)</li> <li>• Chlorambucil (category 3)</li> <li>• Rituximab (category 3)</li> </ul>
Patients age <65 years without significant comorbidities	<b>Ibrutinib (IMBRUVICA®) (category 1)</b>	<ul style="list-style-type: none"> <li>• Bendamustine + an anti-CD20 monoclonal antibody (category 2A)</li> <li>• FCR (fludarabine + cyclophosphamide + rituximab)<sup>§</sup> (category 2A)</li> <li>• FR (fludarabine + rituximab)<sup>  </sup> (category 2A)</li> <li>• HDMP + rituximab (category 2B)</li> <li>• Venetoclax + obinutuzumab (category 2B)</li> <li>• Pentostatin, cyclophosphamide, rituximab (category 3)</li> </ul>
Suggested treatment for first-line therapy in CLL/SLL with del 17p/TP53 mutation		
All patients	<b>Ibrutinib (IMBRUVICA®) (category 2A)</b>  Venetoclax + obinutuzumab (category 2A)	<ul style="list-style-type: none"> <li>• Alemtuzumab +/- rituximab (category 2A)</li> <li>• HDMP + rituximab (category 2A)</li> <li>• Obinutuzumab (category 2A)</li> </ul>

<sup>†</sup>See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for complete list of regimens.

<sup>‡</sup>Bendamustine + anti-CD20 MAB is not recommended for frail patients.

<sup>§</sup>FCR is appropriate first-line treatment for young, fit patients with mutated IGHV.

<sup>||</sup>FR is not recommended for CLL with del(11q).

## Categories of Evidence/Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

## Categories of Preference<sup>¶</sup>

**Preferred intervention:** Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

**Other recommended intervention:** Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

**Useful in certain circumstances:** Other interventions that may be used for selected patient populations (defined with recommendation).

<sup>¶</sup>All recommendations in the NCCN Guidelines are considered appropriate.

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CLL=chronic lymphocytic leukemia, del=deletion, MAB=monoclonal antibody, SLL=small lymphocytic lymphoma.

## IMPORTANT SAFETY INFORMATION (CONT'D)

### WARNINGS AND PRECAUTIONS (CONT'D)

IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

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

## IMPORTANT SAFETY INFORMATION (CONT'D)

### WARNINGS AND PRECAUTIONS (CONT'D)

**Infections:** Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

**Cytopenias:** Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

**Cardiac Arrhythmias:** Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

**Hypertension:** Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

**Second Primary Malignancies:** Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

**Tumor Lysis Syndrome:** Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

**Embryo-Fetal Toxicity:** Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 20\%$ ) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)<sup>#</sup>, diarrhea (41%), anemia (38%)<sup>#</sup>, neutropenia (35%)<sup>#</sup>, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions ( $\geq 5\%$ ) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)<sup>#</sup>, thrombocytopenia (16%), and pneumonia (14%).

Approximately 7% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included pneumonia (1.1%), hemorrhage (1%), atrial fibrillation (0.9%), rash (0.7%), diarrhea (0.6%), neutropenia (0.5%), sepsis (0.4%), thrombocytopenia (0.4%), interstitial lung disease (0.3%), and bruising (0.2%). Nine percent of patients had a dose reduction due to adverse reactions.

<sup>#</sup>Treatment-emergent decreases (all grades) were based on laboratory measurements.

### DRUG INTERACTIONS

**CYP3A Inhibitors:** Modify IMBRUVICA® dose as described in USPI sections 2.4 and 7.1.

**CYP3A Inducers:** Avoid coadministration with strong CYP3A inducers.

### SPECIFIC POPULATIONS

**Hepatic Impairment** (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.



## Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA® (ibrutinib) tablets, for oral use

### INDICATIONS AND USAGE

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

**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion:** IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

### CONTRAINDICATIONS

None

### WARNINGS AND PRECAUTIONS

**Hemorrhage:** Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,124 patients exposed to IMBRUVICA in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding [see *Clinical Studies (14) in Full Prescribing Information*].

**Infections:** Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA in clinical trials [see *Adverse Reactions*]. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

**Cytopenias:** Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

**Cardiac Arrhythmias:** Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see *Dosage and Administration (2.3) in Full Prescribing Information*].

**Hypertension:** Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

**Second Primary Malignancies:** Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

**Tumor Lysis Syndrome:** Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

**Embryo-Fetal Toxicity:** Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations*].

## IMBRUVICA® (ibrutinib)

### ADVERSE REACTIONS

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

- Hemorrhage [see *Warnings and Precautions*]
- Infections [see *Warnings and Precautions*]
- Cytopenias [see *Warnings and Precautions*]
- Cardiac Arrhythmias [see *Warnings and Precautions*]
- Hypertension [see *Warnings and Precautions*]
- Second Primary Malignancies [see *Warnings and Precautions*]
- Tumor Lysis Syndrome [see *Warnings and Precautions*]

**Clinical Trials Experience:** Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and four randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS, and iLLUMINATE) in patients with CLL/SLL (n=1,506 total and n=781 patients exposed to IMBRUVICA). Patients with creatinine clearance (CrCl)  $\leq$  30 mL/min, AST or ALT  $\geq$  2.5 x ULN (upper limit of normal), or total bilirubin  $\geq$  1.5x ULN (unless of non-hepatic origin) were excluded from these trials. Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil, HELIOS included 574 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab, and iLLUMINATE included 228 randomized patients with treatment naïve CLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab.

The most commonly occurring adverse reactions in patients with CLL/SLL receiving IMBRUVICA ( $\geq$ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, rash, musculoskeletal pain, bruising, nausea, fatigue, pyrexia, hemorrhage, and cough.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia. Adverse reactions leading to dose reduction occurred in approximately 7% of patients.

**Study 1102:** Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of  $\geq$  10% with a median duration of treatment of 15.6 months are presented in Tables 1 and 2.

**Table 1: Non-Hematologic Adverse Reactions in  $\geq$  10% of Patients with CLL/SLL (N=51) in Study 1102**

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2

**IMBRUVICA® (ibrutinib)**

**Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102 (continued)**

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies	10	2 <sup>†</sup>
Vascular disorders	Hypertension	16	8

<sup>†</sup>One patient death due to histiocytic sarcoma.

**Table 2: Treatment-Emergent\* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102**

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

\* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

**RESONATE:** Adverse reactions and laboratory abnormalities described below in Tables 3 and 4 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

**Table 3: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE**

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
<b>Gastrointestinal disorders</b>				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
<b>General disorders and administration site conditions</b>				
Pyrexia	24	2	15	2 <sup>†</sup>
<b>Infections and infestations</b>				
Upper respiratory tract infection	16	1	11	2 <sup>†</sup>
Pneumonia*	15	12 <sup>†</sup>	13	10 <sup>†</sup>
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
<b>Skin and subcutaneous tissue disorders</b>				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
<b>Nervous system disorders</b>				
Headache	14	1	6	0
Dizziness	11	0	5	0
<b>Injury, poisoning and procedural complications</b>				
Contusion	11	0	3	0
<b>Eye disorders</b>				
Vision blurred	10	0	3	0

Subjects with multiple events for a given adverse reaction (ADR) term are counted once only for each ADR term.

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The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

\* Includes multiple ADR terms

<sup>†</sup> Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

**Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE**

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 8% in the ofatumumab arm) occurred in patients.

**RESONATE-2:** Adverse reactions described below in Table 5 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

**Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2**

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
<b>Gastrointestinal disorders</b>				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
<b>Eye disorders</b>				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
<b>Skin and subcutaneous tissue disorders</b>				
Rash*	21	4	12	2
Bruising*	19	0	7	0
<b>Infections and infestations</b>				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	22	0	15	0
<b>General disorders and administration site conditions</b>				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
<b>Vascular disorders</b>				
Hypertension*	14	4	1	0
<b>Nervous system disorders</b>				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

\* Includes multiple ADR terms

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**HELIOS:** Adverse reactions described below in Table 6 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

**Table 6: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS**

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
<b>Blood and lymphatic system disorders</b>				
Neutropenia*	66	61	60	56 <sup>†</sup>
Thrombocytopenia*	34	16	26	16
<b>Skin and subcutaneous tissue disorders</b>				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
<b>Gastrointestinal disorders</b>				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
<b>General disorders and administration site conditions</b>				
Pyrexia	25	4	22	2
<b>Vascular disorders</b>				
Hemorrhage*	19	2 <sup>†</sup>	9	1
Hypertension*	11	5	5	2
<b>Infections and infestations</b>				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
<b>Metabolism and nutrition disorders</b>				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

\* Includes multiple ADR terms

<1 used for frequency above 0 and below 0.5%

<sup>†</sup> Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

**iLLUMINATE:** Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

**Table 7: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE**

Body System Adverse Reaction <sup>§</sup>	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
<b>Blood and lymphatic system disorders</b>				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
<b>Skin and subcutaneous tissue disorders</b>				
Rash*	36	3	11	0
Bruising*	32	3	3	0

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**Table 7: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)**

Body System Adverse Reaction <sup>§</sup>	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
<b>Gastrointestinal Disorders</b>				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal Pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	27	1	12	0
<b>Injury, Poisoning and Procedural Complications</b>				
Infusion related reaction	25	2	58	8
<b>Vascular disorders</b>				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
<b>Infections and Infestations</b>				
Pneumonia*	16	9	9	4 <sup>†</sup>
Upper Respiratory Tract Infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0
<b>Metabolism and Nutrition Disorders</b>				
Hyperuricemia	13	1	0	0
<b>Cardiac Disorders</b>				
Atrial Fibrillation	12	5	0	0
<b>General Disorders and Administration Site Conditions</b>				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
<b>Psychiatric disorders</b>				
Insomnia	12	0	4	0

<sup>§</sup> The data are not an adequate basis for comparison of ADR rates between treatment arms.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

\* Includes multiple ADR terms

<sup>†</sup> Includes one event with a fatal outcome.

**Additional Important Adverse Reactions: Cardiac Arrhythmias:** In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.5% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 9% versus 1.4% and for Grade 3 or greater was 4.1% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

**Diarrhea:** In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for



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any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

**Visual Disturbance:** In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (6% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome [see *Warnings & Precautions*]
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasia, panniculitis
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

## DRUG INTERACTIONS

**Effect of CYP3A Inhibitors on Ibrutinib:** The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see *Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see *Dosage and Administration (2.4) in Full Prescribing Information*]. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see *Dosage and Administration (2.4) in Full Prescribing Information*].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

**Effect of CYP3A Inducers on Ibrutinib:** The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see *Clinical Pharmacology (12.3) in Full Prescribing Information*].

## USE IN SPECIFIC POPULATIONS

**Pregnancy: Risk Summary:** IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities [see *Data*]. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S.

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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:** Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 20 times the exposure in patients with CLL/SLL administered the dose of 420 mg daily. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.8 times the exposure (AUC) in patients with CLL/SLL administered the dose of 420 mg daily.

**Lactation: Risk Summary:** There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

**Females and Males of Reproductive Potential: Pregnancy Testing:** Conduct pregnancy testing in females of reproductive potential prior to initiating IMBRUVICA therapy.

**Contraception: Females:** Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. 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.

**Males:** Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

**Pediatric Use:** The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

**Geriatric Use:** Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥ 75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

**Hepatic Impairment:** Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely [see *Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information*].

## PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- **Hemorrhage:** Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see *Warnings and Precautions*].
- **Infections:** Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see *Warnings and Precautions*].
- **Cardiac Arrhythmias:** Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see *Warnings and Precautions*].
- **Hypertension:** Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see *Warnings and Precautions*].
- **Second primary malignancies:** Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see *Warnings and Precautions*].

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- *Tumor lysis syndrome*: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see *Warnings and Precautions*].
- *Embryo-fetal toxicity*: Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA [see *Warnings and Precautions*].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see *Dosage and Administration (2.1) in Full Prescribing Information*].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see *Dosage and Administration (2.6) in Full Prescribing Information*].
- Advise patients of the common side effects associated with IMBRUVICA [see *Adverse Reactions*]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION .
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see *Drug Interactions*].
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see *Adverse Reactions*].

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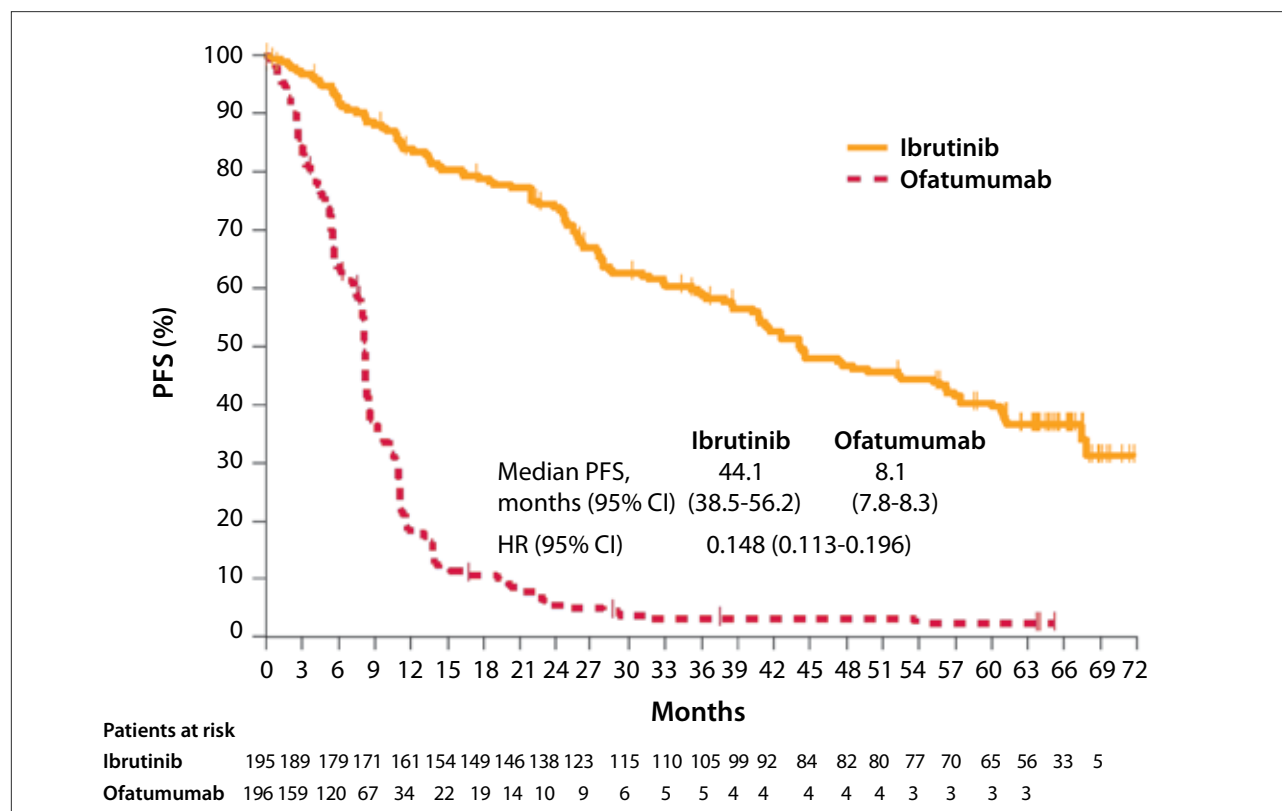
## Final Analysis From RESONATE: Six-Year Follow-Up in Patients With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma on Ibrutinib

Ibrutinib, an inhibitor of Bruton tyrosine kinase (BTK), is approved for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).<sup>1</sup> The multicenter, open-label, phase 3 RESONATE trial (A Phase 3 Study of Ibrutinib [PCI-32765] Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia) compared once-daily oral therapy with ibrutinib (420 mg) vs intravenous ofatumumab (300 mg initial dose, followed by 11 doses at 2000 mg administered throughout 24 weeks) in 391 patients with previously

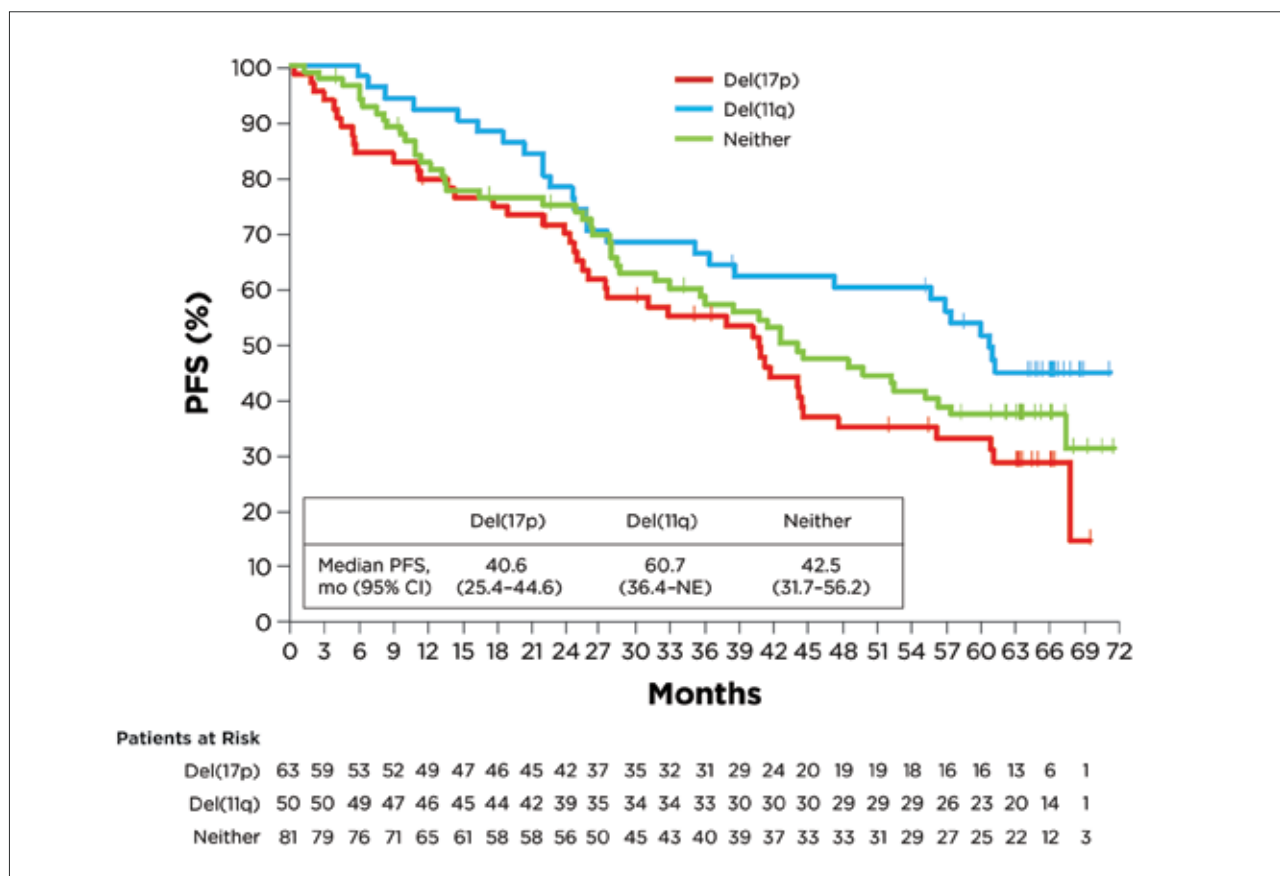
treated CLL/SLL. Enrolled patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had measurable disease, and were not candidates for purine analogue therapy. The primary endpoint was progression-free survival (PFS). Patients were a median age of 67 years (range, 30-88 years), 58% had Rai stage III/IV disease, and 46% had received at least 3 prior therapies. After a median follow-up of 9.4 months, the median PFS was not reached with ibrutinib vs 8.1 months with ofatumumab (hazard ratio [HR], 0.22;  $P < .001$ ).<sup>2</sup> Ibrutinib was also associated

with superior overall survival (OS; HR, 0.43;  $P < .001$ ), reducing the risk of death by 57%. The objective response rate (ORR) was 42.6% with ibrutinib vs 4.1% with ofatumumab ( $P < .001$ ).

Long-term efficacy in the RESONATE study was evaluated after a median follow-up of 65.3 months (range, 0.3+ to 71.6 months) in the ibrutinib arm and 65.6 months (range, 0.1-73.9 months) in the ofatumumab arm.<sup>3</sup> The median duration of treatment was 41.0 months with ibrutinib and 5.3 months with ofatumumab. The most common reasons for discontinuation of ibrutinib were disease



**Figure 1.** Progression-free survival in the intention-to-treat population of the phase 3 RESONATE trial of ibrutinib vs ofatumumab in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. Data are shown for the final analysis, performed after a median of 6 years of follow-up. HR, hazard ratio; PFS, progression-free survival; RESONATE, A Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. Adapted from Barr PM et al. ASCO abstract 7510. *J Clin Oncol.* 2019;37(18 suppl).<sup>3</sup>



**Figure 2.** Progression-free survival according to del(17p) and del(11q) status in the phase 3 RESONATE trial of ibrutinib vs ofatumumab in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. Data are shown from the final analysis, after a median of 6 years of follow-up. Del(11q), deletion 11q; Del(17p), deletion 17p; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; RESONATE, A Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. Adapted from Barr PM et al. ASCO abstract 7510. *J Clin Oncol.* 2019;37(18 suppl).<sup>3</sup>

### NCCN UPDATE Updates in the Use of Ibrutinib From the NCCN Guidelines

The latest guidelines from the National Comprehensive Cancer Network (NCCN) reflect several updates for the recommended use of ibrutinib in patients with CLL or SLL (Version 5.2019). Ibrutinib plus obinutuzumab was added as a category 2B, other recommended regimen, for patients with CLL or SLL who do not have del(17p) or the *TP53* mutation and who are frail or have significant comorbidities (regardless of age). (Ibrutinib monotherapy is a category 1 recommendation for these patients.) For patients younger than 65 years without significant comorbidities, ibrutinib was changed from a category 2A to a category 1 recommendation for first-line therapy. Also for these patients, ibrutinib plus rituximab was added as a category 2B, other recommended regimen. Regarding toxicity, the guidelines now state that invasive fungal infections have been rarely reported early after initiation of ibrutinib. The guidelines have no recommendation for routine prophylaxis.

progression (37%) and adverse events (AEs; 16%). Among the patients in the ofatumumab arm, 68% crossed over to the ibrutinib arm during the study.

In the intention-to-treat population, the median PFS was 44.1 months with ibrutinib vs 8.1 months with ofatumumab (HR, 0.148; 95% CI, 0.113-0.196; Figure 1). The median OS was 67.7 months vs 65.1 months (HR, 0.810; 95% CI, 0.602-1.091).

Several secondary analyses evaluated the outcomes according to the patients' mutational status. In the subset of patients with the chromosome 17p deletion (del[17p]), chromosome 11q deletion (del[11q]), *TP53* mutation, or unmutated immunoglobulin

heavy chain variable (*IGHV*), the median PFS was 44.1 months with ibrutinib vs 8.0 months with ofatumumab (HR, 0.110; 95% CI, 0.080-0.152). Among patients in the ibrutinib arm, the longest median PFS was observed in patients with del(11q), at 60.7 months. The median PFS was 40.6 months in patients with del(17p) and 42.5 months in patients lacking del(11q) or del(17p) (Figure 2). In an exploratory analysis, the median PFS was 40.6 months in patients with del(17p) and/or the *TP53* mutation vs 56.9 months in patients with del(11q). The median PFS was not reached in patients who lacked del(17p), del(11q), and the *TP53* mutation. The median PFS was 48.4 months in patients with mutated *IGHV* and 49.7 months for those with unmutated *IGHV*.

In the ibrutinib arm, infections of grade 3 or higher occurred in 87 patients (45%), with a median time of onset of 7.0 months (range, 0.0-63.0 months). Hypertension of any grade occurred in 41 patients treated with

ibrutinib (21%). The median time of onset of hypertension was 13.8 months (range, 1.0-54.0 months).

## References

1. Imbruvica [package insert]. Sunnyvale, CA: Pharmacia-cyclics LLC; 2016.
2. Byrd JC, Brown JR, O'Brien S, et al; RESONATE

### ABSTRACT SUMMARY Allogeneic Stem Cell Transplantation Is Effective for Patients With Lymphoma and Chronic Lymphocytic Leukemia Following Treatment With Targeted Small-Molecule Inhibitors

A retrospective, single-center study evaluated the safety, engraftment rate, risk for graft-vs-host disease, and survival associated with small-molecule inhibitor treatment prior to allogeneic stem cell transplant (Abstract 7550). The trial enrolled 49 patients with CLL or lymphoma who had undergone allogeneic stem cell transplant after receiving a small-molecule inhibitor (ibrutinib, idelalisib, or venetoclax). Most patients had high-risk genetic features. The median number of prior treatments was 4 (range, 1-11). In all patients, engraftment was successful, with no evidence of failure or need for delay. One-year OS was 77%, and 1-year PFS was 68%. The median OS was similar in the subgroups of patients with CLL, mantle cell lymphoma, or follicular lymphoma ( $P=.79$ ). Based on multivariate analysis, the presence of acute grade 3/4 graft-vs-host disease and refractory disease were predictors of inferior PFS and OS. The presence of high-risk genetic characteristics did not affect outcomes.

Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.

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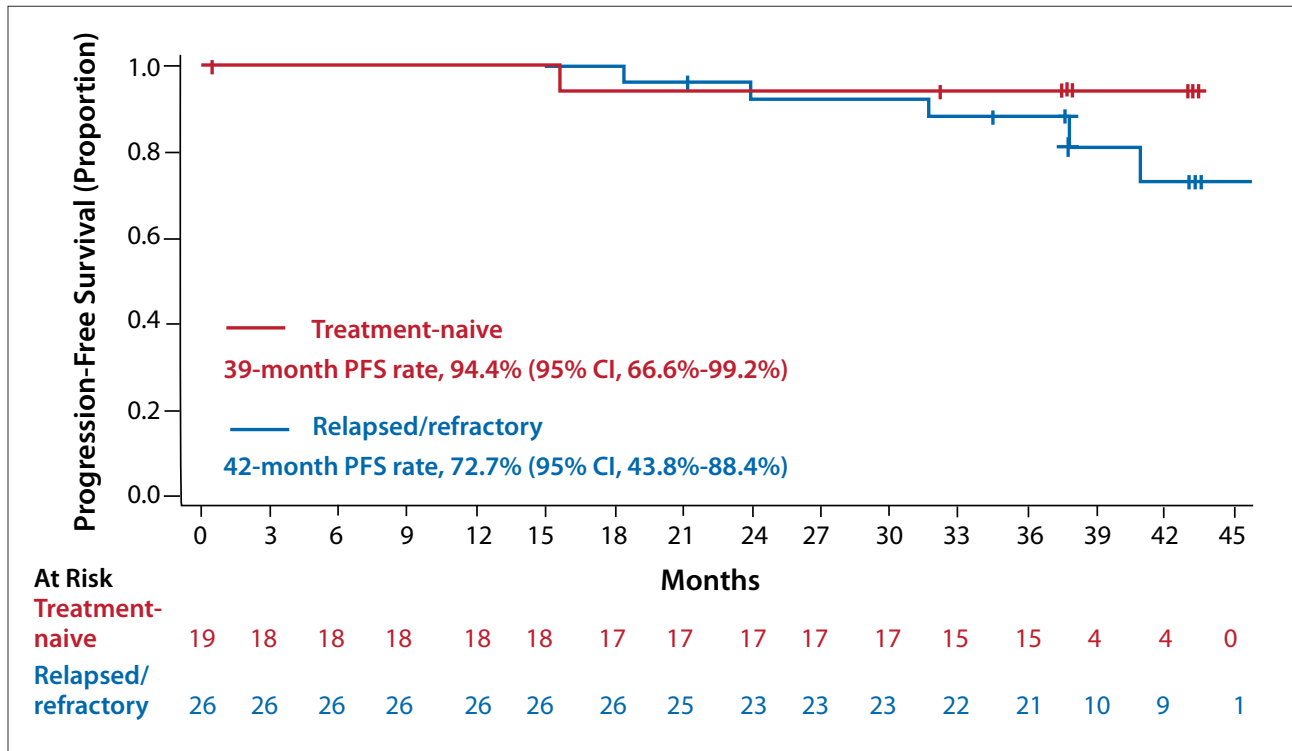
## Acalabrutinib With Obinutuzumab in Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia: Three-Year Follow-Up

**A**calabrutinib is a covalent inhibitor of BTK that has shown minimal off-target binding. In a phase 1/2 study of 61 patients with relapsed CLL, acalabrutinib showed no dose-limiting toxicities and yielded an ORR of 95%.<sup>1</sup> Results in treatment-naive patients with CLL have also demonstrated acceptable safety and high response rates.<sup>2</sup> Acalabrutinib was evaluated in combination with obinutuzumab in a phase 1/2 study of patients with CLL.<sup>3</sup> The trial enrolled 19 treatment-naive CLL/SLL patients ages 65 years or older, as well as younger patients who were ineligible for chemoimmunotherapy. Twenty-six patients with relapsed or refractory disease were also enrolled. Patients had a diagnosis of CLL or SLL with mea-

asurable disease.<sup>4</sup> They had an ECOG performance status of 0 to 2, and they met the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria for treatment. Patients received acalabrutinib at 100 mg twice daily or 200 mg once daily in 28-day cycles. Patients also received obinutuzumab beginning with cycle 2. The cycle 2 loading dose of obinutuzumab was administered at 100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15. During cycles 3 to 7, patients received obinutuzumab (1000 mg, day 1). Minimal residual disease (MRD) was measured using multicolor flow cytometry with a  $10^{-4}$  cutoff.

Among the 45 enrolled patients, the median age was approximately 62 years (range, 42-76 years). Most

patients were male, and all patients had an ECOG performance status of 0 or 1. Approximately half of patients had bulky disease. Rai stage III/IV disease was observed in 53% of treatment-naive patients and 27% of previously treated patients. Among the 26 patients with relapsed or refractory disease, the median number of prior therapies was 1 (range, 1-9). Nearly all of the patients had a diagnosis of CLL, with the exception of 1 treatment-naive SLL patient. After a median follow-up of approximately 3.5 years, 78% of patients remained on treatment. Acalabrutinib was discontinued by 11% of treatment-naive patients and 31% of previously treated patients, most commonly owing to an AE. The full course of obinutuzumab



**Figure 3.** In a trial of acalabrutinib plus obinutuzumab in chronic lymphocytic leukemia, the median progression-free survival was not reached among treatment-naive patients or those with relapsed/refractory disease after 3 years of follow-up. PFS, progression-free survival. Adapted from Woyach JA et al. ASCO abstract 7500. *J Clin Oncol.* 2019;37(18 suppl).<sup>3</sup>

was completed by 89% of treatment-naive patients and 100% of previously treated patients.

In the treatment-naive group, the ORR was 95%, including a partial response (PR) rate of 63.2% and a complete response (CR) rate of 31.6%. The median time to a PR or CR was 2.8 months (range, 2.8-2.8 months), and the median time to a CR was 18.4 months (range, 5.6-32.3 months). Among patients with a PR at 22 months' follow-up, 3 demonstrated a CR at 39 months of follow-up, a finding that is consistent with deepening responses over time. Based on bone marrow analysis, 5 of the 19 treatment-naive patients (26%) had undetectable MRD at the beginning of cycle 12. Among the 26 patients with relapsed or refractory disease at enrollment, 84.6% experienced a PR and 7.7% had a CR, yielding an ORR of 92%. The median time to response was 2.8 months (range, 2.7-21.4 months), and the median time to CR was 12.9

months (range, 10.2-15.7 months). Based on bone marrow analysis, 4 patients with relapsed or refractory disease at baseline (15%) were MRD-negative on day 1 of cycle 12. The median durations of response and PFS were not reached in the subgroups of treatment-naive or previously treated patients. The 39-month PFS rate was 94.4% (95% CI, 66.6%-99.2%) in treatment-naive patients (Figure 3). The 42-month PFS rate was 72.7% (95% CI, 43.8%-88.4%) in previously treated patients. MRD negativity was more common among treatment-naive patients (26% vs 15%). MRD responses in the peripheral blood were generally maintained over time, as observed through cycle 36.

Among the entire cohort, the most common AEs of any grade included upper respiratory tract infection (73%), increased weight (72%), and maculopapular rash (66%). The most common grade 3/4 AEs were decreased neutrophil count (24%)

and syncope (11%), followed by decreased platelet count, cellulitis, and increased weight (9% each). The most common serious AE was cellulitis (9%), followed by diarrhea, dyspnea, pneumonia, pyrexia, and syncope (4% each). AEs leading to discontinuation included grade 1 vomiting, grade 3 maculopapular rash, grade 3 diarrhea, grade 3 lung adenocarcinoma, and grade 3 squamous cell carcinoma, each observed in 1 patient. Richter transformation was observed in 1 treatment-naive and 2 previously treated patients. No grade 5 AEs occurred. Bleeding events of any grade occurred in 71%.

One patient with relapsed or refractory disease at baseline had a history of atrial fibrillation, and this patient developed atrial fibrillation prior to the 2-year follow-up.<sup>5</sup> No additional atrial fibrillation events were observed as part of the 3.5-year follow-up. Hypertension of any grade occurred in 40% of patients.

### ABSTRACT SUMMARY Atrial Fibrillation in Patients With CLL Treated With Ibrutinib: Assessing Prediction Models and Clinical Outcomes

A retrospective study evaluated 3 risk prediction models for the development of atrial fibrillation in patients with CLL treated with ibrutinib (Abstract 7522). The study included 298 patients with a combined 565 years of exposure to ibrutinib. The median number of prior therapies was 1 (range, 0-15). The median Italian Risk Score was 2 (range, 0-9), the median Shanafelt Risk Score was 3.5 (range, 0-7), and the median Framingham AF Risk Score was 8.4% (range, 0.1%-30%). After a median follow-up of 24 months (range, 0-70 months), treatment-emergent atrial fibrillation occurred in 51 patients (17%). Treatment-emergent atrial fibrillation was best predicted by the Italian Risk Score. The 2-year risk for atrial fibrillation was 6% for a score of 0, 8% for a score of 1 to 2, 26% for a score of 3 to 4, and 47% for a score of 5 or higher. Six patients (12%) permanently discontinued ibrutinib after atrial fibrillation. No thrombotic strokes occurred in the patients with atrial fibrillation. However, 2 major bleeding events were observed.

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## Long-Term Follow-Up of Previously Untreated Patients With Chronic Lymphocytic Leukemia Treated With Ofatumumab and Chlorambucil: Final Analysis of the Phase 3 COMPLEMENT 1 Trial

The phase 3 COMPLEMENT 1 trial (Ofatumumab + Chlorambucil vs Chlorambucil Monotherapy in Previously Untreated Patients With Chronic Lymphocytic Leukemia) evaluated chlorambucil with or without ofatumumab in treatment-naïve patients with CLL.<sup>1</sup> The final analysis of the COMPLEMENT 1 study was based on 5 years of follow-up.<sup>2</sup> The study included treatment-naïve patients with CLL with active disease and an ECOG performance status of 0 to 2 who were not eligible for fludarabine-based treatment. Prior to randomization, patients were stratified by disease stage, age, and ECOG performance status. The trial randomly assigned 447 patients to receive chlorambucil (10 mg/m<sup>2</sup>, days 1-7) for 12 cycles of 28 days, either as monotherapy or with the addition of ofatumumab (300 mg, day 1 of cycle 1; 1000 mg, day 8 of cycle 1; then 1000 mg, day 1 of cycles 2-12).

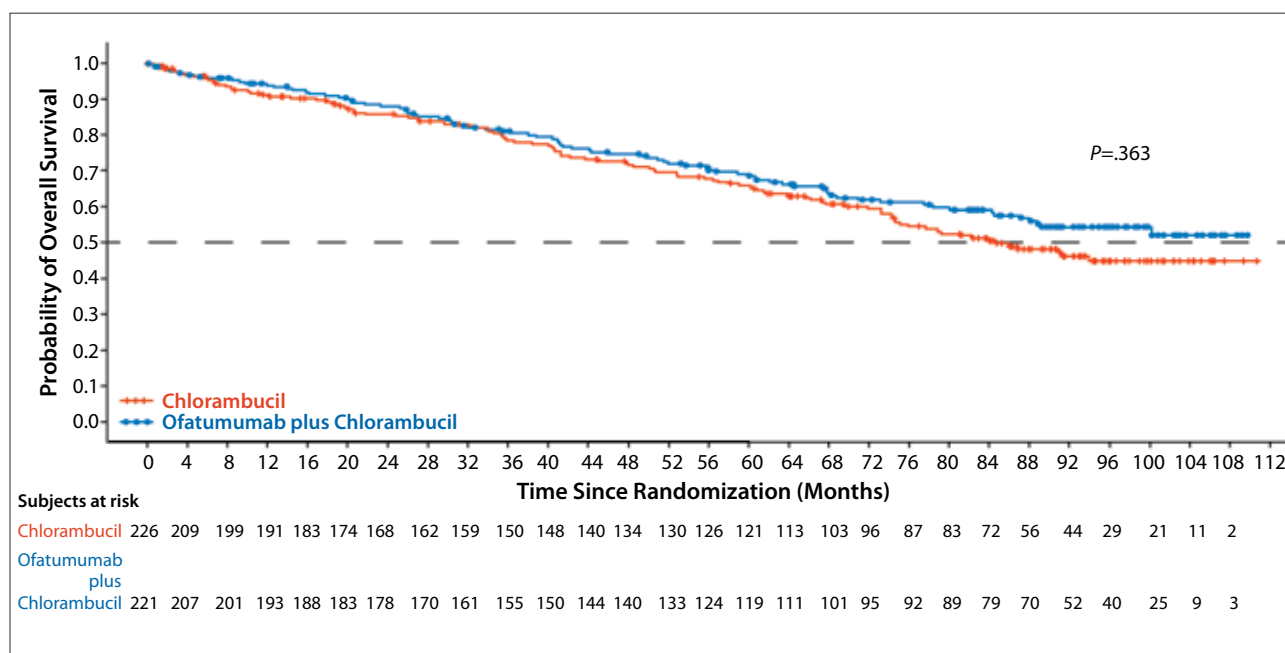
At the time of the 5-year analysis,

183 patients (41%) had died, 245 (55%) had withdrawn from the study, and 19 (4%) had completed 5 years of follow-up. The most common reason for withdrawal was study termination by the sponsor (33%). Patient and disease characteristics were well balanced between the 2 treatment arms. Patients had a median age of 69 years (range, 35-92 years), and 69% were ages 65 years or older. Most patients (63%) were male, and 40% had Rai stage III/IV disease. *IGHV* sequence homology exceeding 98% was observed in 56% of patients, and the most common chromosomal aberration was deletion 13q, seen in 53%.

The median OS was not estimable with ofatumumab plus chlorambucil vs 84.7 months with chlorambucil monotherapy (HR, 0.88; 95% CI, 0.65-1.17; *P* = .363; Figure 4). OS was similar among subgroups based on Rai or Binet stage disease at study entry. There were 10 on-treatment deaths (5 in each arm). Median PFS was 23.4

months in the ofatumumab plus chlorambucil arm vs 14.7 months in the chlorambucil monotherapy arm (HR, 0.61; 95% CI, 0.49-0.76; *P* < .001). After discontinuation of study treatment, a greater proportion of patients in the chlorambucil monotherapy arm received further anticancer therapy (66% vs 56%), and subsequent therapy was initiated sooner among patients in the chlorambucil monotherapy arm (median, 486 vs 743 days).

No new safety concerns were raised with the combination treatment. AEs of any grade were observed in 96% of patients in the ofatumumab plus chlorambucil arm vs 90% in the chlorambucil monotherapy arm. AEs of grade 3 or higher occurred in 64% vs 48%, respectively. The most common AEs of grade 3 or higher were neutropenia (26% in the combination arm vs 15% in the monotherapy arm), thrombocytopenia (5% vs 10%), and pneumonia (9% vs 5%). Serious AEs that were considered drug-related were



**Figure 4.** A final analysis of the probability of overall survival among patients with treatment-naive chronic lymphocytic leukemia who received chlorambucil plus ofatumumab or chlorambucil alone in the phase 3 COMPLEMENT 1 trial. COMPLEMENT 1, Chlorambucil Plus Ofatumumab Versus Chlorambucil Alone in Previously Untreated Patients With Chronic Lymphocytic Leukemia. Adapted from Offner F et al. ASCO abstract 7528. *J Clin Oncol.* 2019;37(18 suppl).<sup>2</sup>

observed in 15% of the combination arm vs 13% of the monotherapy arm.

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## TRANSCEND CLL 004: Minimal Residual Disease Negative Responses After Lisocabtagene Maraleucel (JCAR017), a CD19-Directed CAR T-Cell Product, in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

**L**isocabtagene maraleucel, also known as JCAR017, is a chimeric antigen receptor (CAR) T-cell product directed at CD19.<sup>1</sup> The lisocabtagene maraleucel product is created by separately expanding the patient's engineered CD4-positive and CD8-positive cells. The 2 cell types are then administered in precise 1-to-1 doses. Lisocabtagene maraleucel was evaluated in the phase 1 TRANSCEND CLL 004 trial (Study Evaluating Safety and Efficacy of JCAR017 in Subjects

With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL] or Small Lymphocytic Lymphoma [SLL]) of patients with relapsed or refractory CLL/SLL.<sup>2</sup> The study enrolled patients who were ineligible for treatment with a BTK inhibitor or had an inadequate response to this therapy. Patients had an ECOG performance status of 0 or 1. Patients with high-risk cytogenetic factors (eg, the *TP53* mutation, unmutated *IGHV*) had failed at least 2 prior therapies, including a BTK inhibitor.

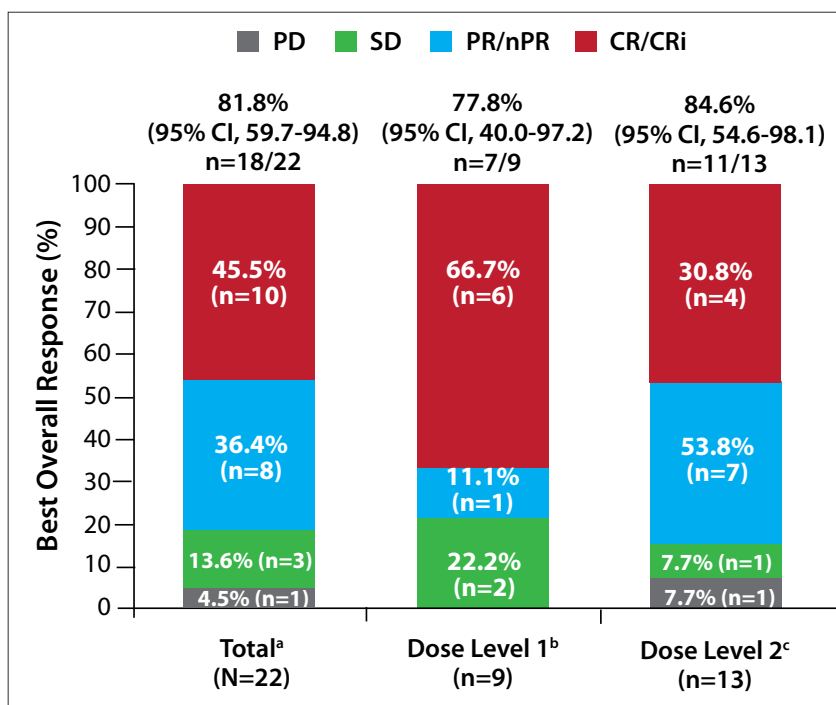
Patients at standard risk had failed at least 3 previous therapies. The study used a modified toxicity probability interval to guide dose escalation. Patients were monitored for dose-limiting toxicities, and responses were assessed based on iwCLL 2008 criteria.<sup>3</sup> The primary objectives were to determine the recommended dose of lisocabtagene maraleucel and to evaluate safety. Bridging therapy was allowed after enrollment and leukapheresis. Measurable disease was reconfirmed prior to initiation of



study therapy. Lymphodepletion was carried out by daily fludarabine (30 mg/m<sup>2</sup>) and cyclophosphamide (300 mg/m<sup>2</sup>) administered for 3 days. Within 2 to 7 days after lymphodepletion chemotherapy, lisocabtagene maraleucel was administered at 2 dose levels: 50 × 10<sup>6</sup> CAR T cells and 100 × 10<sup>6</sup> CAR T cells. MRD was assessed in the blood by flow cytometry, using a cutoff of 10<sup>-4</sup>, and in the bone marrow by next-generation sequencing, using a cutoff of 10<sup>-6</sup>.

The trial enrolled 9 patients into the lower dose level cohort and 14 into the higher dose level cohort. The 23 patients had a median age of 66 years (range, 49-79 years), and 48% were male. Bulky disease was observed in 35% of patients, and 65% had Rai stage III/IV disease. Fewer patients in the lower dose level cohort had received bridging therapy (56% vs 86%) or had high-risk genetics (67% vs 93%).

After a median follow-up of 9 months (minimum, 1 month), the best ORR in 22 patients was 81.8%, including a rate of 36.4% for PR/nodular PR and of 45.5% for CR/CR with incomplete blood count recovery (Figure 5). Undetectable MRD was seen in 75% of patients based on blood analysis and in 65% based on bone marrow analysis. An objective response was reported in 68% of patients (15/22), and 60% (12/20) had undetectable MRD in the bone marrow by day 30. Responses deepened over time in 27% of patients (6/22). Durable responses were observed at 6 months after administration of CAR T-cell therapy in most patients. Among 6 patients who experienced a CR at 6 months, this response was still evident at 9 months in 5 patients and beyond 12 months in 3 patients. Pharmacokinetic and pharmacodynamic profiling showed a rapid decrease in CD19-positive cells within 2 to 3 weeks after administration of the study treatment. The higher dose of 100 × 10<sup>6</sup> CAR T cells was chosen for the phase 2 portion of the study. A separate cohort of patients in the phase 1 portion of the study is receiving lisocabtagene maraleucel in combination with ibrutinib.



**Figure 5.** Best overall response among patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma treated with lisocabtagene maraleucel in the phase 1 cohort of the TRANSCEND CLL 004 trial. <sup>a</sup>Evaluable for response was defined as patients with a pretreatment assessment and at least 1 postbaseline assessment. Evaluable for MRD was defined as patients with detectable MRD at baseline. One patient was not evaluable for response. <sup>b</sup>50 × 10<sup>6</sup> CAR T+ cells. <sup>c</sup>100 × 10<sup>6</sup> CAR T+ cells. CAR, chimeric antigen receptor; CR, complete response; CRi, complete response with incomplete blood count recovery; MRD, minimal residual disease; nPR, nodular partial response; PD, progressive disease; PR, partial response; SD, stable disease; TRANSCEND CLL 004, Study Evaluating Safety and Efficacy of JCAR017 in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Adapted from Siddiqi T et al. ASCO abstract 7501. *J Clin Oncol*. 2019;37(18 suppl).<sup>2</sup>

#### ABSTRACT SUMMARY Long-Term Effects of Ibrutinib on Blood Pressure in Patients With Chronic Lymphocytic Leukemia

A retrospective study evaluated the effects of long-term treatment with ibrutinib on blood pressure in patients with CLL (Abstract e19009). The study included 150 patients with CLL treated with ibrutinib in clinical trials from 2010 through 2015. The median follow-up was 3 years. Hypertension was reported in 44% of patients at baseline, and 40% were receiving antihypertensive treatment prior to initiation of ibrutinib. New-onset hypertension was diagnosed in 65% of patients who had no prior diagnosis of hypertension. Thirty-two percent of patients began antihypertensive therapy or received additional antihypertensive treatment. The median systolic blood pressure was 130 mm Hg at baseline and increased to 144 mm Hg at 5 years (mean increase, 7.2 mm Hg;  $P < .001$ ). The subgroup of patients with a systolic blood pressure of less than 130 mm Hg at baseline experienced a mean increase of 15.7 mm Hg ( $P < .001$ ). An increase in systolic blood pressure of at least 10 mm Hg occurred in 74% of patients.

Throughout both patient cohorts, the most common treatment-emergent AEs of any grade were anemia (83%), cytokine release syndrome (74%), and thrombocytopenia (74%). The most common AEs of grade 3 or higher included anemia (78%), thrombocytopenia (70%), and neutropenia (57%). High-grade AEs were more common in patients who received the higher dose of CAR T cells. Two dose-limiting toxicities were observed, both in the higher-dose cohort. They consisted of grade 4 hypertension in 1 patient, and a combination of grade 3 encephalopathy, grade 3 muscle weakness, and grade 4 tumor lysis syndrome in the other.

Across the 2 cohorts, the most

common serious treatment-emergent AEs of any grade included cytokine release syndrome (26%), pyrexia (17%), encephalopathy (13%), febrile neutropenia (13%), and pneumonia (13%). Six patients died during the study: 4 from disease progression, 1 from respiratory failure that was unrelated to lisocabtagene maraleucel treatment, and 1 from an unknown cause. Across the 2 dose cohorts, cytokine release syndrome of any grade was observed in 74% of patients. Grade 3 cytokine release syndrome occurred in 2 patients receiving the higher dose vs no patients receiving the lower dose. Grade 3/4 tumor lysis syndrome was observed in 1 patient (11%) receiving the lower

dose and 3 patients (21%) receiving the higher dose.

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## Phase 1/2 Trial of Cirmtuzumab and Ibrutinib: Planned Analysis of Phase 1 CLL Cohorts

**C**irmtuzumab is a humanized antibody that binds with high specificity to the receptor tyrosine kinase–like orphan receptor 1 (ROR1). ROR1 is found on cancer stem cells and is expressed on malignant B cells in the vast majority of patients with CLL.<sup>1</sup> In a study of 26 patients with CLL, cirmtuzumab exhibited acceptable safety, without dose-limiting toxicities.<sup>2</sup> The antibody had a long plasma half-life and inhibited ROR1 signaling.

The combination of cirmtuzumab plus ibrutinib was evaluated in a phase 1/2 study of patients with CLL/SLL or mantle cell lymphoma.<sup>3</sup> In the dose-finding portion of the trial, 3 patients were enrolled per cohort. Cirmtuzumab was administered every 2 weeks for the first 5 doses, followed by monthly administration, for a total duration of 1 year. The cirmtuzumab dose was based on weight, ranging from 2 mg/kg to 16 mg/kg per dose; or was administered in a fixed dose of 300 mg or 600 mg. During the first month, patients received cirmtuzumab monotherapy to allow for assessment

of biomarkers. Ibrutinib (420 mg daily) was administered for 48 weeks.<sup>4</sup> Patients with prior exposure to a BTK inhibitor were excluded from study enrollment.

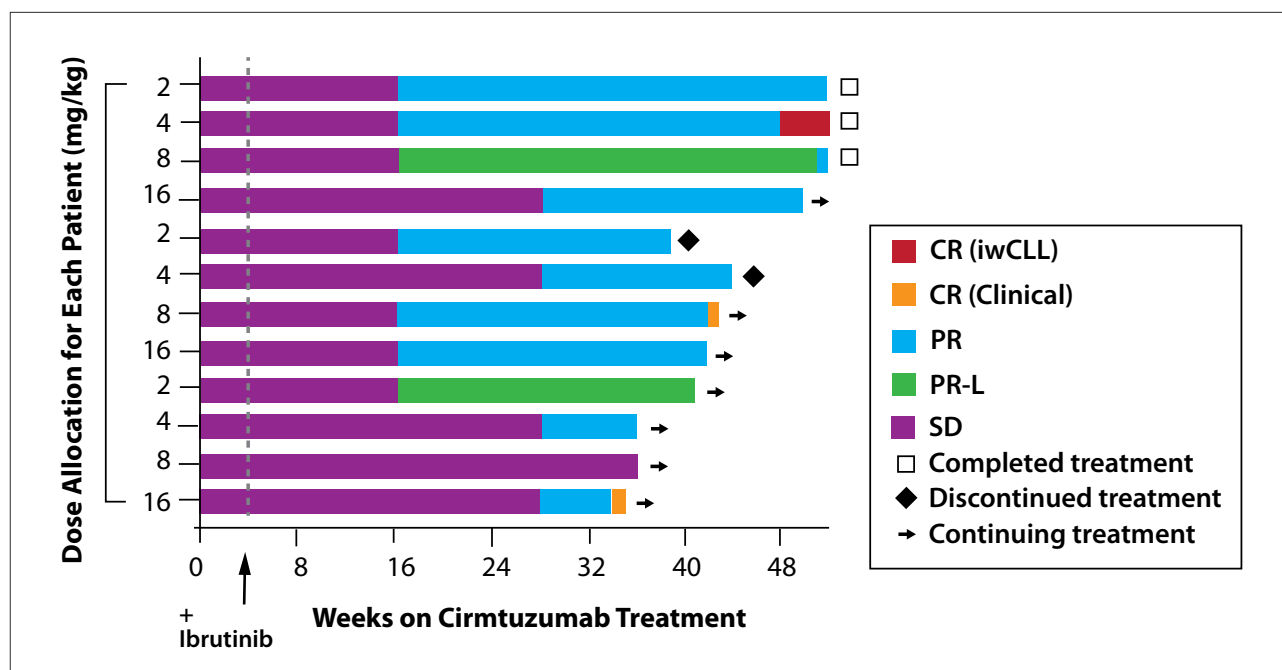
The patients' median age was 69 years (range, 57-86 years), and 3 patients were treatment-naïve. Among the 9 patients with relapsed or refractory disease, the median number of prior therapies was 2 (range, 1-5). In the safety cohort of 18 patients, the most common treatment-emergent AEs for the duration of the study were contusions (50%), arthralgia (33%), and fatigue (28%). Two patients discontinued treatment owing to AEs that were unrelated to study treatment.

Results for the 12 patients evaluable for efficacy are shown in Figure 6. The ORR was 91.7%. ROR1 receptor occupancy was superior among patients who received the higher doses of cirmtuzumab. Among 3 patients who completed the 1-year planned treatment course, 1 patient with CLL demonstrated a CR (based on iwCLL criteria).<sup>5</sup> Two patients—1 with CLL and 1 with mantle cell lymphoma—

had a clinical CR, based on negative imaging and normalization of absolute lymphocyte count, with bone marrow assessment pending. Concurrent administration of cirmtuzumab with ibrutinib appeared to attenuate the lymphocytosis that can be seen with ibrutinib monotherapy. The recommended dose of cirmtuzumab chosen for further study was 600 mg (given with 420 mg daily of ibrutinib), based on safety, efficacy, pharmacokinetics, and pharmacodynamics.

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**Figure 6.** Response to cirtuzumab among patients with chronic lymphocytic leukemia in a phase 1 cohort. CR, complete response; iwCLL, International Workshop on CLL criteria; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Adapted from Choi MY et al. ASCO abstract 7527. *J Clin Oncol.* 2019;37(18 suppl).<sup>3</sup>

## Effect of Fixed-Duration Venetoclax Plus Obinutuzumab on Progression-Free Survival, and Rates and Duration of Minimal Residual Disease Negativity in Previously Untreated Patients With Chronic Lymphocytic Leukemia and Comorbidities

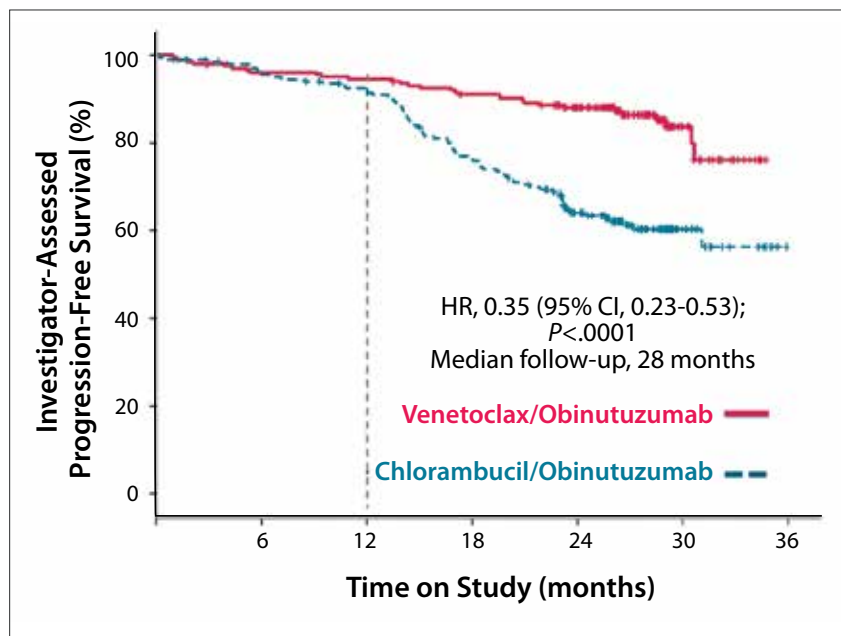
CLL and SLL disproportionately affect older patients, and many of these patients have comorbidities that preclude the administration of standard therapeutic regimens. The CLL11 trial (A Study of Obinutuzumab [RO5072759 (GA101)] With Chlorambucil in Patients With Previously Untreated Chronic Lymphocytic Leukemia [Stage 1a]) evaluated chlorambucil therapy, with or without an anti-CD20 antibody, among patients with treatment-naïve CLL. The study enrolled patients with a Cumulative Illness Rating Scale (CIRS) score exceeding 6 or an estimated creatinine clearance of 30 mL to 69 mL/min.<sup>1,2</sup> At baseline, the 781 patients had a median age of 73 years, a median CIRS score of 8

(range, 0-22), and a median creatinine clearance of 62 mL/min.

The median PFS was 31.1 months with chlorambucil plus obinutuzumab vs 11.1 months with chlorambucil monotherapy (HR, 0.21; 95% CI, 0.16-0.28;  $P < .0001$ ).<sup>2</sup> The median OS was not reached vs 66.7 months (HR, 0.68; 95% CI, 0.49-0.94;  $P = .0196$ ).

Venetoclax is a BCL2 inhibitor that has shown promise in combination with obinutuzumab as therapy for treatment-naïve patients with CLL and coexisting conditions.<sup>3</sup> The combination of obinutuzumab plus venetoclax was evaluated in patients with CLL in the international, open-label phase 3 CLL14 trial (A Study to Compare the Efficacy and Safety of Obinutuzumab + Venetoclax [GDC-

0199] Versus Obinutuzumab + Chlorambucil in Participants With Chronic Lymphocytic Leukemia).<sup>4,5</sup> The study enrolled previously untreated patients with CLL. All patients had comorbidities, as well as a CIRS score exceeding 6 and/or an estimated creatinine clearance of less than 70 mL/min. The study randomly assigned patients to receive 6 cycles of venetoclax plus obinutuzumab followed by 6 cycles of venetoclax monotherapy, or 6 cycles of chlorambucil plus obinutuzumab followed by 6 cycles of chlorambucil monotherapy. All treatment cycles lasted 28 days, so both arms received a maximum of 12 months of treatment for CLL. MRD negativity was defined as less than  $10^{-4}$  malignant cells. The primary endpoint was PFS.



**Figure 7.** Progression-free survival according to the investigator among patients with treatment-naïve chronic lymphocytic leukemia who received fixed-duration venetoclax plus obinutuzumab vs chlorambucil plus obinutuzumab. HR, hazard ratio. Adapted from Fischer K et al. ASCO abstract 7502. *J Clin Oncol.* 2019;37(18 suppl).<sup>4</sup>

#### ABSTRACT SUMMARY Second Cancer Incidence in CLL Patients Receiving BTK Inhibitors

A retrospective study assessed the incidence of secondary cancers in patients with CLL treated with a BTK inhibitor at a single institution (Abstract 7511). The incidence of a second primary malignancy was correlated with baseline patient factors using the Fine-Gray model. Richter transformation and nonmelanoma skin cancer were excluded. The study evaluated data for 691 patients with CLL who received ibrutinib or acalabrutinib. The median follow-up was 44 months (range, 1-90 months). Half of the patients discontinued treatment with the BTK inhibitor, and the median duration of treatment was 46 months. Sixty-four patients (9.3%) were diagnosed with a second, invasive cancer, yielding a standardized incidence ratio of 2.2 (95% CI, 1.7-2.9). Based on a multivariate analysis, the factors associated with an increased risk for secondary malignancy included smoking ( $P=.0003$ ) and low levels of CD8-positive cells ( $P<.0001$ ). At 5 years, the cumulative incidence ratio for secondary cancers was 10.8 (95% CI, 8.0-14.0). The standardized incidence ratios were highest for melanoma (5.3), acute myeloid leukemia/myelodysplastic syndrome (4.0), bladder cancer (3.7), lung cancer (3.5), and kidney cancer (2.9).

The study randomly assigned 432 patients into the 2 treatment arms. The patients' median age was 71 to 72 years, and the median CIRS score was 8 to 9. The median estimated creatinine clearance was 65.2 mL/min

in the venetoclax/obinutuzumab arm and 67.5 mL/min in the chlorambucil/obinutuzumab arm. In each arm, 43% of patients had Binet stage C disease. In the venetoclax arm, 61% had unmutated *IGHV*, 12% had *TP53*

deletion and/or mutation, 9% had del(17p), and 18% had del(11q). In the control arm, 59% had unmutated *IGHV*, 12% had the *TP53* deletion and/or mutation, 7% had del(17p), and 20% had del(11q).

The ORR was 85% with venetoclax plus obinutuzumab vs 71% with chlorambucil plus obinutuzumab ( $P<.0001$ ). The median PFS was also longer with venetoclax plus obinutuzumab (HR, 0.35; 95% CI, 0.23-0.53;  $P<.0001$ ; Figure 7). Two-year PFS was 88% with the venetoclax combination vs 64% with the chlorambucil combination. OS was similar for the 2 arms ( $P=.52$ ). The addition of venetoclax to obinutuzumab improved the likelihood of achieving MRD negativity. The rate of MRD negativity in the peripheral blood was 76% in the venetoclax/obinutuzumab arm vs 35% in the chlorambucil/obinutuzumab arm ( $P<.001$ ). The rate of CR with undetectable MRD was 42% vs 14% ( $P<.001$ ). Similarly, bone marrow MRD was more likely with the venetoclax combination (57% vs 17%), as was the achievement of MRD negativity in CR (34% vs 11%). Low MRD levels persisted for several months after the cessation of venetoclax plus obinutuzumab. Based on next-generation sequencing of peripheral blood at 3 months after completion of treatment, MRD of less than  $10^{-6}$  was achieved in 42% of patients in the venetoclax/obinutuzumab arm vs 7% in the control arm.

A grade 3/4 hematologic AE occurred in 60% of patients in the venetoclax/obinutuzumab arm and 55% in the chlorambucil/obinutuzumab arm. Neutropenia was the most common of these events, seen in 53% vs 48%. Infusion-related reactions occurred in 9% vs 10% of patients. Infections and infestations were observed in 18% vs 15%. Metabolic and nutritional disorders were observed in 12% vs 6%. Five patients (2%) in the venetoclax/obinutuzumab arm and 4 patients (2%) in the control arm died during the active treatment phase of the study. In addition, 11 patients (5%) in the

venetoclax arm and 4 (2%) in the chlorambucil arm died after completion of study treatment.

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## ABSTRACT SUMMARY Occurrence of Other Cancers in Patients With Chronic Lymphocytic Leukemia and Mutations in Protection of Telomeres 1 (POT1) Gene

Mutation of the protection of telomeres 1 (*POT1*) gene in patients with CLL is associated with uncapping of the telomere ends, resulting in deleterious chromosomal rearrangements. In a study of 1467 patients with CLL treated at a single institution, 52 patients (3.5%) had a mutated *POT1* gene (Abstract 7529). These patients tended to be male (71.2%) and relatively young (median age, 59 years). More than two-thirds of patients with the mutation had Binet stage A disease. Based on fluorescence in situ hybridization, common chromosomal abnormalities included deletion 13q (del[13q]) in 33% and del(11q) in 21.2%. *IGHV* was unmutated in 69% of patients. The most common DNA mutations in the 52 patients with *POT1* mutations were found in *NOTCH1* (44%), *TP53* (27%), and *SF3B1* (23%). Other malignancies, exclusive of nonmelanoma skin cancer, were observed in 19 of the patients (37%). These other malignancies had been diagnosed before CLL in 12 patients (23%) and after the diagnosis of CLL in 7 (13%). Common secondary malignancies included prostate cancer (n=6), melanoma (n=5), and kidney cancer (n=4).

## Effect of Dose Modifications on Response to Duvelisib in Patients With Relapsed/Refractory CLL/SLL in the DUO Trial

The open-label phase 3 DUO trial (A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL) evaluated duvelisib vs ofatumumab in patients with relapsed or refractory CLL/SLL.<sup>1</sup> The median PFS was superior with duvelisib (13.3 vs 9.9 months; HR, 0.52;  $P < .0001$ ), as was ORR (74% vs 45%;  $P < .0001$ ). The standard dose of duvelisib was 25 mg twice daily, administered continuously. To manage treatment-emergent AEs, the dose could be interrupted or reduced to 15 mg, 10 mg, or 5 mg administered twice daily.

A retrospective analysis of data from the DUO trial assessed the rate of duvelisib dose modifications and their impact on response.<sup>2</sup> The 158 patients in the duvelisib arm had a median exposure to duvelisib of 11.6 months (range, 0.2-36.8 months). The median dose intensity was 97.7 (range, 34.7-100) out of a maximum score of 100. Dose interruptions were more

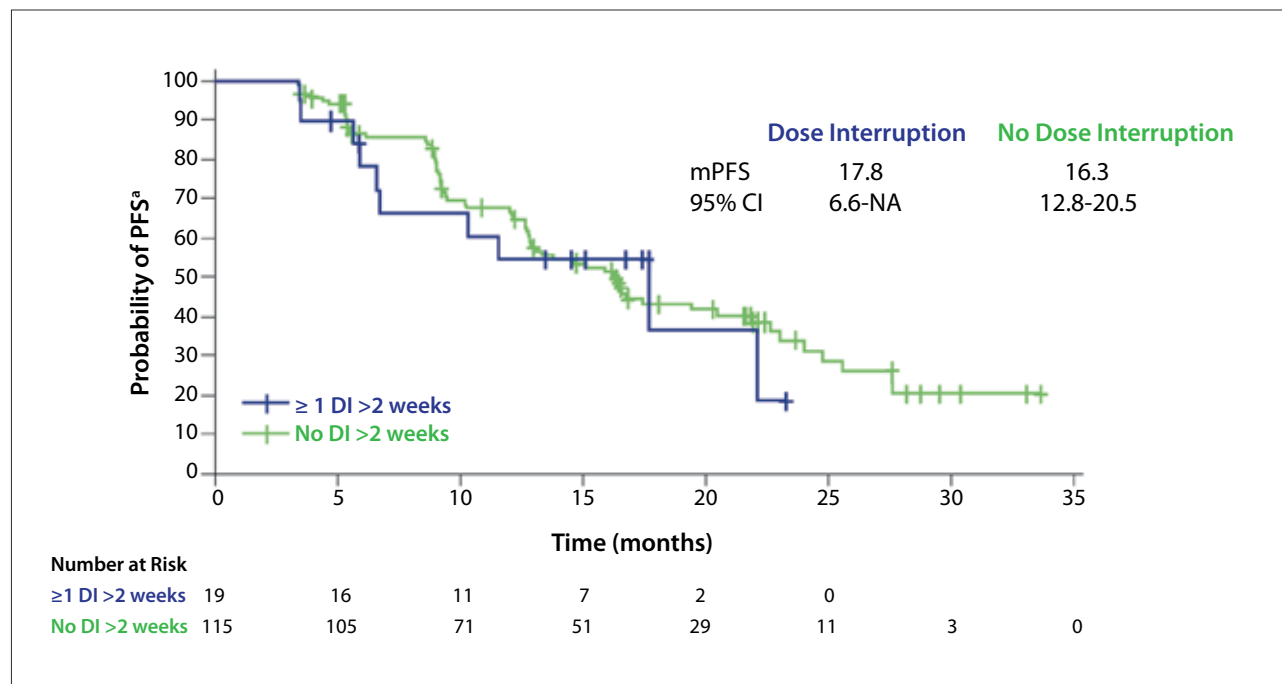
common than dose reductions (80% vs 27%). The most common AEs of special interest that led to dose interruptions were diarrhea/colitis (28%), infection (27%), and cutaneous reactions (13%), whereas those that led to dose reductions were diarrhea/colitis (8%), cutaneous reactions (4%), and neutropenia (4%).

Among the 118 responders in the duvelisib arm, the median time to first response was 1.9 months, and the estimated median duration of response was 11.1 months. In 50 patients, the dose interruption lasted longer than 1 week. Treatment then resumed for at least 3 weeks. Among these patients, 84% maintained or improved their response. A similar observation was made in the cohort of patients who had a dose interruption lasting longer than 2 weeks. The median PFS was 17.8 months for the subset of patients with a dose interruption lasting at least 1 week vs 16.3 months for those who did not. The same durations of median

PFS, 17.8 months and 16.3 months, were shown for patients who did or did not have a dose interruption lasting at least 2 weeks (Figure 8). Among patients with a dose reduction during the first 3 months of treatment, the median PFS was 22.1 months, vs 15.1 months among those without a dose reduction. Similarly, median PFS was longer in patients who had a dose reduction during the first 6 months of study treatment vs those who did not (22.1 vs 17.4 months). The study authors suggested that duvelisib dose interruptions and dose reductions can be used to manage treatment-emergent AEs in patients with relapsed or refractory CLL/SLL.

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**Figure 8.** The impact of dose interruptions of duvelisib on the probability of progression-free survival among patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma treated in the phase 3 DUO trial. DI, dose interruption; DUO, A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL; mPFS, median progression-free survival; NA, not available; PFS, progression-free survival. Adapted from Flinn IW et al. ASCO abstract 7523. *J Clin Oncol.* 2019;37(18 suppl).<sup>2</sup>

## Phase 2 Study of Acalabrutinib in Ibrutinib-Intolerant Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

**A**calabrutinib monotherapy was evaluated in a multicenter, international, open-label phase 2 trial of patients with CLL who had developed intolerance to ibrutinib during prior treatment.<sup>1</sup> The ACE-CL-208 trial (A Study of ACP-196 [Acalabrutinib] in Subjects With Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy) enrolled patients with CLL who had received at least 1 prior systemic treatment, with ibrutinib as the most recent prior therapy. Intolerance was defined as persistent grade 3 or 4 AEs that led to discontinuation of ibrutinib, or grade 2 AEs related to ibrutinib that persisted for at least 2 weeks or recurred at least twice, despite dose reduction or discontinuation. Patients developed disease progression after discontinu-

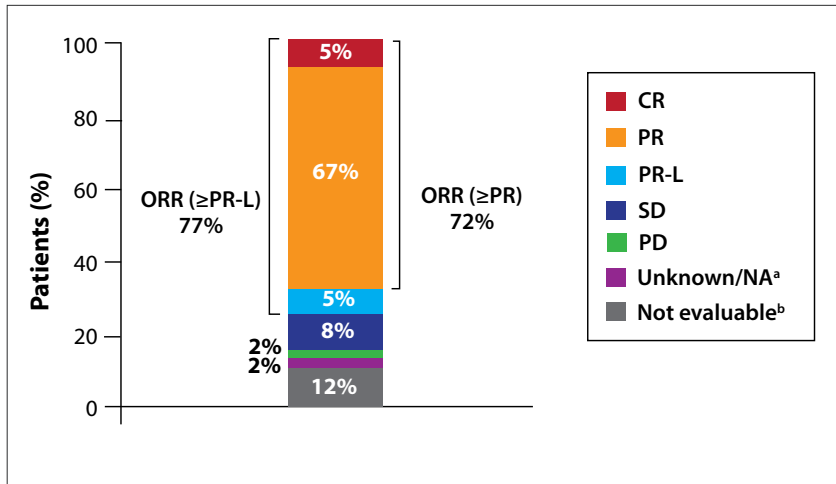
ation of ibrutinib. Enrolled patients were not candidates for treatment with a purine analogue-based regimen. Acalabrutinib (100 mg) was administered twice daily in 28-day cycles until disease progression or unacceptable toxicity. AE severity was graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

The 60 patients in the study were a median age of 70 years (range, 43-88 years), and 63% were male. Thirty-two percent had bulky lymph nodes, and 52% had Rai stage III/IV disease. Genetic risk factors included unmutated *IGHV* in 79%, *del(17p)* in 28%, and *del(11q)* in 23%. Mutations in phospholipase C gamma 2 (*PLCG2*) or *BTK* were each observed in 4% of patients. Among 55 patients

tested, 52% had wild-type *BTK* and *PLCG2* genes. The 60 patients had received a median of 2 prior therapies (range, 1-10). The median duration of prior ibrutinib therapy was 6 months (range, 1-56 months).

After a median follow-up of 23 months, 48 patients (80%) remained on the study. The investigator-assessed ORR was 72%, including a CR rate of 5%. The inclusion of PR with lymphocytosis increased the investigator-assessed ORR to 77% (Figure 9). Among 17 patients with *del(17p)*, the ORR was 71% (95% CI, 44%-90%). The median duration of response, the median PFS, and the median OS were not reached.

Most AEs were grade 1 or 2. The most common AEs of grade 3 or higher were pneumonia (10%), neutropenia



**Figure 9.** Response according to the investigator among patients with relapsed/refractory chronic lymphocytic leukemia treated with acalabrutinib. The response was assessed according to iwCLL 2008 criteria. <sup>a</sup>For 1 patient, the investigator reported the result as unknown/NA. <sup>b</sup>Seven patients (12%) terminated the study before the first disease assessment at cycle 3, day 28. CR, complete response; iwCLL, International Workshop on CLL; NA, not applicable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Adapted from Rogers KA et al. ASCO abstract 7530. *J Clin Oncol.* 2019;37(18 suppl).<sup>1</sup>

(8%), reduced neutrophil count (7%), decreased lymphocyte count (7%), and lymphocytosis (7%). Serious AEs of any grade were observed in 35% of patients and included pneumonia (10%) and syncope (3%). AEs led to treatment discontinuation in 12% of patients; these events consisted of pneumonia in 2 patients, as well

as diarrhea, headache, endometrial cancer, arthralgia, and subdural hematoma, each observed in 1 patient. Grade 5 AEs included pneumonia (n=2), bronchopulmonary aspergillosis (n=1), and ventricular fibrillation (n=1), but none of these events were considered related to acalabrutinib treatment. Events of clinical inter-

est included bleeding (62%), cardiac events (15%), hypertension (12%), and grade 3/4 infections (17%).

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## Outcomes in Chronic Lymphocytic Leukemia Patients With *NOTCH1* Signaling Pathway Mutations

**D**ysregulation of the *NOTCH1* pathway plays a key role in CLL pathogenesis, affecting cell growth, division, and apoptosis.<sup>1,2</sup> Activating mutations in *NOTCH1* are common in leukemic cells and associated with a poor prognosis. Less is known regarding how genes that regulate *NOTCH1* contribute to the development and progression of CLL.

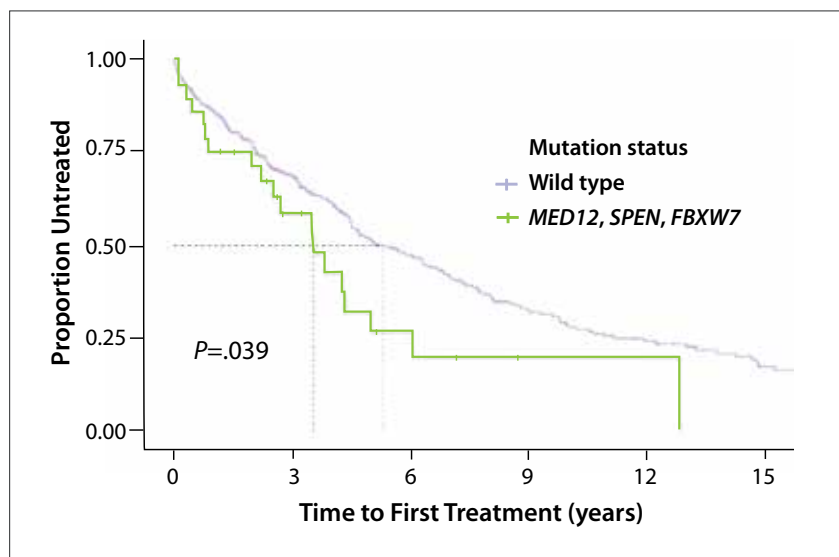
A retrospective study conducted at a single center assessed the relationship between mutations in genes that regulate *NOTCH1* and outcomes in patients with CLL.<sup>3</sup> The study included patients with a diagnosis of CLL who had data for next-generation sequencing, based on a lymphoid-specific gene panel. Genes of interest

included mediator complex subunit 12 (*MED12*), F-box and WD repeat domain containing 7 (*FBXW7*), and spen family transcriptional repressor (*SPEN*). Mutations in these genes can lead to increased activity of *NOTCH1*. Outcomes in patients with mutations in *MED12*, *FBXW7*, and *SPEN* were pooled and then compared with outcomes in patients with the wild-type genes, as well as wild-type *NOTCH1*.

The study analyzed data from 557 patients who underwent next-generation sequencing. It found that 33 (5.9%) had a mutation in *MED12*, *FBXW7*, or *SPEN*; 63 (11.3%) had a mutation in *NOTCH1*; and 465 (83.5%) had wild-type copies of these genes. Ten patients (1.8%) had

*MED12* mutations, 17 (3.1%) had *FBXW7* mutations, and 9 (1.6%) had mutations in the *SPEN* gene. More than half of the patients had Rai stage 0 or 1 disease.

Compared with the wild-type cohort, patients with mutations in *NOTCH1* or the regulatory genes of interest were more likely to have CD38-positive disease, trisomy 12, and unmutated *IGHV*. The time to first treatment was significantly reduced among patients who had a mutation in *MED12*, *FBXW7*, or *SPEN* compared with patients who lacked mutations in these genes and in *NOTCH1* ( $P=.039$ ; Figure 10). Based on a univariate analysis, the time to first treatment was decreased among



**Figure 10.** Time to first treatment according to *NOTCH1* signaling pathway mutations among patients with chronic lymphocytic leukemia. Adapted from Helbig D et al. ASCO abstract 7524. *J Clin Oncol.* 2019;37(18 suppl).<sup>3</sup>

patients with CD38-positive disease, unmutated *IGHV*, Zap-70 expression, del(11p), del(17p), the *TP53* mutation, or a mutation in any of the *NOTCH1* regulatory genes of interest (*MED12*, *FBXW7*, or *SPEN*). However, multivariate analysis showed that only unmutated *IGHV* remained as an independent predictor of reduced time to first treatment ( $P < .001$ ).

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## Highlights in Chronic Lymphocytic Leukemia From the 2019 American Society of Clinical Oncology Annual Meeting: Commentary

Susan M. O'Brien, MD

At the 2019 American Society of Clinical Oncology Annual Meeting, several presentations in chronic lymphocytic leukemia (CLL) explored new treatment options, such as lisocabtagene maraleucel, venetoclax plus obinutuzumab, and acalabrutinib. Long-term follow-up data were presented for ibrutinib.

### CAR T-Cell Therapy

Dr Tanya Siddiqi presented results from the phase 1 component of the TRANSCEND CLL 004 trial, which evaluated lisocabtagene maraleucel, a chimeric antigen receptor (CAR) T-cell therapy, in patients with CLL.<sup>1</sup> There are CAR T-cell therapies approved by the US Food and Drug Administration (FDA) for pediatric acute lymphoblastic leukemia and adult lymphoma, but none for CLL.<sup>2</sup> A unique characteristic of this product, also known as liso-cel, is

that it uses equal amounts of CD4 and CD8 T cells. With most of the other CAR T-cell therapies, this ratio is not fixed. Researchers performing preclinical work on liso-cel suggested that efficacy and toxicity might be better with a product that uses a 1-to-1 ratio of CD4 to CD8.<sup>3</sup> The phase 1 cohort included 23 patients with CLL, so it was not a large number. The patients were heavily pretreated, with a median of 5 prior therapies. All patients had received prior ibrutinib, and more than half had received prior venetoclax. This study continues the theme of using CAR T-cell therapy in the most advanced patients who have few other options.

Two dose-limiting toxicities were reported: a case of grade 4 hypertension and a case of grade 3 encephalopathy, grade 3 muscle weakness, and grade 4 tumor lysis syndrome. Cytokine-release syndrome occurred in 73.9%

of patients, but only 2 cases were grade 3 or higher. That low incidence of severity is promising. The main toxicity concerns with CAR T-cell therapy are grade 3 to 4 cytokine release syndrome and neurotoxicity. Grade 3/4 neurologic events occurred in 21.7% of patients.

Liso-cel was associated with a high response rate of 81.9%, with a complete response (CR) rate of 45.5%. Many patients had undetectable minimal residual disease (MRD) at day 30.

Data from this phase 1 trial are encouraging. The study investigators selected the higher dose for evaluation in the phase 2 portion of the trial. The efficacy and toxicity were similar between the 2 doses. However, early data showed that the CAR T cells persisted longer with the higher dose, which could be important for efficacy in the long-term.



### Venetoclax and Obinutuzumab

CLL-14 evaluated the effect of fixed-duration venetoclax plus the anti-CD20 agent obinutuzumab in patients with previously untreated CLL.<sup>4</sup> Approximately a year ago, results of the MURANO trial were presented.<sup>5</sup> The MURANO trial compared venetoclax plus the anti-CD20 therapy rituximab vs bendamustine plus rituximab in relapsed CLL. A hallmark of the MURANO trial was that it tested a time-limited small-molecule therapy. Patients in the bendamustine plus rituximab arm received the standard 6-cycle regimen. Patients in the venetoclax plus rituximab arm received 6 cycles of the antibody and then single-agent venetoclax for 2 years total. This strategy was novel because the small molecules, including venetoclax, are administered as continuous therapy until the patient becomes intolerant to treatment or develops progressive disease. The MURANO trial showed high response rates with the novel strategy. Results presented at the 2018 American Society of Hematology meeting showed that after a year of follow-up among all patients off-therapy, most of the remissions persisted.<sup>6</sup>

The CLL-14 study also evaluated a time-limited strategy. The antibody was changed to obinutuzumab, which the investigators thought might be more potent. The trial enrolled more than 400 patients, with a median age older than 70. The eligibility criteria did not specify older patients, but it required a high comorbidity score and/or reduced renal function. These eligibility criteria are used in all of this group's trials that are directed at older, less-fit patients. The patients were randomly assigned to treatment with venetoclax or chlorambucil, both in combination with obinutuzumab for 6 cycles, followed by single-agent venetoclax or chlorambucil alone for 6 cycles. In contrast to the MURANO trial, single-agent venetoclax was given for only 1 year. The idea was that in

this population of previously untreated patients, those likely to achieve undetectable MRD would do so in a shorter period compared with patients who have relapsed disease.

The study's primary endpoint of progression-free survival (PFS) was significantly better with venetoclax plus obinutuzumab. The median PFS was not reached. The MRD undetectable rate in the peripheral blood was 76% with venetoclax plus obinutuzumab vs only 35% with chlorambucil plus obinutuzumab. This rate is high for chlorambucil, and likely reflects the addition of obinutuzumab. Bone marrow MRD was undetectable in 57% of patients receiving venetoclax plus obinutuzumab vs only 17% in those receiving the chlorambucil-based regimen. These high rates of MRD negativity were exciting to see in patients who stopped therapy after 1 year. The median time off treatment was approximately 19 months, and most of the remissions achieved with venetoclax plus obinutuzumab were still persisting at that time. It will be interesting to see how durable these remissions are. It is an important advantage to be able to administer small molecules in a time-limited fashion.

The combination regimen of venetoclax plus obinutuzumab was well tolerated. The most frequent adverse event (AE) was neutropenia, which developed in 53% of the venetoclax arm and 48% of the chlorambucil arm. Chlorambucil is a weak chemotherapy, so myelosuppression is minimal. With venetoclax, neutropenia can sometimes prevent use of the full dose of 400 mg.

### BTK Inhibitors

Dr Kerry Rogers presented results of a trial evaluating acalabrutinib in patients with CLL who were intolerant to ibrutinib.<sup>7</sup> Ibrutinib was the first Bruton tyrosine kinase (BTK) inhibitor approved by the FDA, and it is the only one currently approved for CLL. Acalabrutinib is approved for mantle cell lymphoma,<sup>8</sup> but not CLL.

Another BTK inhibitor, zanubrutinib, is undergoing evaluation in clinical trials.<sup>9,10</sup> A putative advantage of next-generation BTK inhibitors is that they may be more potent against BTK than ibrutinib; confirmation remains to be seen. In addition, it is known that they have higher half maximal inhibitory concentration (IC<sub>50</sub>) values for some of the other kinases targeted by ibrutinib. A possible advantage to the higher IC<sub>50</sub> values concerns the drugs' toxicity profiles. It is thought that some of the AEs associated with ibrutinib, such as atrial fibrillation and bleeding problems from platelet dysfunction, are not related to inhibition of BTK, but rather to inhibition of other kinases, such as Tec or the epidermal growth factor receptor. Boys with X-linked agammaglobulinemia are born with mutations in their BTK, but they do not have any bleeding disorders or platelet dysfunction. This suggests that some of the toxicities associated with ibrutinib may be off-target, and are not related to the inhibition of BTK.

An ongoing, randomized head-to-head trial is comparing acalabrutinib vs ibrutinib in relapsed patients with high-risk CLL (defined as having the 17p or 11q deletions).<sup>11</sup> Zanubrutinib is also being studied in a head-to-head comparison with ibrutinib.<sup>9</sup> Data from direct comparison trials of ibrutinib vs the next-generation BTK inhibitors are therefore forthcoming. Currently, it is known that the toxicity profiles differ. Phase 1/2 presentations have shown that a common AE with acalabrutinib is headache, which tends to be minor.<sup>12</sup> Headaches become less common over time, as is seen with diarrhea among patients treated with ibrutinib. The study presented by Dr Rogers evaluated acalabrutinib in patients who could not tolerate ibrutinib owing to either persistent grade 3 or 4 AEs, or grade 2 AEs that persisted or recurred even after the dose was reduced or discontinued. Grade 3 to 4 AEs are uncommon with ibrutinib. It is more common to see persistent or

recurrent grade 2 AEs. Most patients can tolerate grade 2 toxicity for a limited period. Since ibrutinib is given indefinitely, however, even these grade 2 AEs can become intolerable over time. All patients in the trial developed progressive disease after discontinuing ibrutinib.

Acalabrutinib was administered at 100 mg twice daily. Unlike ibrutinib, which is administered once daily, both acalabrutinib and zanubrutinib are administered twice daily. The primary endpoint of the study was overall response. Tolerability was a key secondary endpoint. The trial enrolled 60 patients, who had received a median of 2 prior therapies. The median duration of prior ibrutinib therapy was approximately 6 months, but the duration was much longer for some patients. Not surprisingly, atrial fibrillation was the most frequent AE that led to discontinuation of ibrutinib; others included diarrhea, arthralgia, and rash, which are also known to be associated with ibrutinib.

After a median follow-up of approximately a year and a half, two-thirds of the patients were still receiving acalabrutinib, which shows that they were tolerating treatment well. Approximately half the cases of treatment discontinuation were related to disease progression, and only 10% were due to AEs. The response rate of 77% was not higher than that typically seen with ibrutinib, but it is similar. It is comforting to know that in patients who discontinue ibrutinib because of toxicity, another BTK inhibitor can have very good efficacy. The main AE of interest was atrial fibrillation, which occurred in 3 patients. All episodes were grade 1 to 2. Major bleeding occurred in 2 patients.

The use of acalabrutinib will be an attractive strategy once it is approved by the FDA, certainly for patients who cannot tolerate ibrutinib. Without data from randomized trials, it is difficult to say whether acalabrutinib should be used before ibrutinib. Ibrutinib is a very active drug that is well tolerated

in most patients. The current trial data do not provide an incentive to start treatment with acalabrutinib rather than ibrutinib. One possible exception might be in patients with prior or current atrial fibrillation. It is possible that physicians may elect to use acalabrutinib before ibrutinib in patients who have a history of atrial fibrillation but no recent episodes. There is a chance that atrial fibrillation will be less likely to recur with acalabrutinib vs ibrutinib. However, in patients with atrial fibrillation that is well controlled, treatment with ibrutinib will not necessarily exacerbate the condition.

Hypertension is another AE seen with ibrutinib. The reported frequencies vary, but it appears that hypertension becomes more common with longer durations of treatment. Ibrutinib is administered indefinitely, and hypertension does not always arise early in the treatment course. It stands to reason that the longer patients receive ibrutinib, the more likely they are to develop hypertension. In contrast, there is a decrease in the incidence of the more common AEs, such as diarrhea or rash. To determine the long-term impact of ibrutinib on blood pressure, researchers at the MD Anderson Cancer Center performed a retrospective study of 150 patients treated in clinical trials.<sup>13</sup> The study assessed how many patients developed new-onset hypertension, which was defined as a systolic rate greater than 130 mm Hg and/or a diastolic rate greater than 80 mm Hg on 2 separate visits with no prior history of hypertension or antihypertensive therapy. Preexisting hypertension was seen in 44%, as would be expected in an older population with comorbidities. Forty percent of the patients were receiving antihypertensive therapy before they started ibrutinib. Among patients without a prior diagnosis of hypertension, nearly two-thirds met the study criteria for diagnosis. Only approximately half of these patients were then started on therapy, which

could mean 1 of 2 things. It may be that physicians are undertreating hypertension or failing to recognize it. A more probable explanation is that some of these patients met the criteria based on a rare-time reading. Elevations in blood pressure can be related to stress or other circumstances.

Nearly one third of the patients required initiation of antihypertensive therapy during treatment with ibrutinib. This finding is reasonable and consistent with other studies. The retrospective study also evaluated possible predictors for new hypertension. New onset was not associated with cigarette or tobacco use, obesity, kidney disease, or sleep apnea. Therefore, it was not easy to predict which patients would develop hypertension.

This study highlights the need for clinicians to pay attention to their patients' blood pressure during treatment with ibrutinib. This should be feasible because when patients visit the clinic, they always have their vital signs monitored. In my own practice, I sometimes ask patients receiving long-term ibrutinib to keep a log of blood pressure readings. For example, if I notice that a patient has an elevated blood pressure reading during a visit, and if their next appointment is some time away, I ask him or her to maintain a log of readings to review next time. An isolated abnormality should not be used to initiate treatment, but it is important to recognize hypertension that does require management.

Another important abstract was the final analysis of the RESONATE trial.<sup>14</sup> This trial compared ibrutinib vs the anti-CD20 antibody ofatumumab in patients with relapsed/refractory CLL or small lymphocytic lymphoma, and it led to the full FDA approval of ibrutinib in this setting.<sup>15</sup> Originally, ibrutinib received an accelerated approval based on phase 2 data.<sup>16,17</sup> RESONATE was a confirmatory randomized trial of nearly 400 patients. The data showed that ibrutinib was dramatically better than ofatumumab,

producing much longer durations of PFS. In many of the prior analyses, the median PFS had not been reached for ibrutinib.

The current analysis provided data for 6 years of follow-up; the median follow-up was 65.3 months.<sup>14</sup> The RESONATE trial allowed treatment crossover, and two-thirds of the patients in the ofatumumab arm subsequently received ibrutinib. A sustained PFS benefit was observed with ibrutinib, with the median PFS now at 44 months vs 8 months with ofatumumab. This finding is particularly impressive given that two-thirds of patients in the ofatumumab arm crossed over to the ibrutinib arm. Ibrutinib was associated with very durable remissions, with a median of almost 4 years, in a very heavily pretreated population. The median number of prior regimens was between 3 and 4.

This randomized trial confirmed the phase 2 data, showing that even in a heavily pretreated population, the remissions were durable.<sup>14,17</sup> The ORR was 88% with ibrutinib, a very high rate. CRs are not common with ibrutinib, particularly in the relapsed setting. The rate of CR/CR with incomplete bone marrow recovery was 11%, which is similar to the 10% reported in the phase 2 trial. An interesting finding is that even if the responses are not complete, they are still durable. In some cases, patients are not categorized as a CR based on very minimal disease, for example, a lymph node that measures between 1.5 cm and 2 cm on a computed tomography scan. Therefore, even the partial responses are very deep, with reductions in the lymph node bulk of 90% or 95%. These large reductions in tumor bulk might explain why the responses are so durable.

All-grade hypertension occurred in 21% of patients; it was grade 3 in 9%. As I discussed earlier, in the MD Anderson experience, 32% of patients began treatment for new-onset hypertension. The incidence of hypertension will rise slowly, not

dramatically. Atrial fibrillation was seen in 12% of patients, which mirrors the typical range of 10% to 12% seen in other studies. Major hemorrhage was not common, occurring in only 10% of patients. The main reason for treatment discontinuation was disease progression; 37% of patients discontinued treatment for this reason. AEs led to treatment discontinuation in 16%. Another important aspect of these long-term follow-up trials is that they provide insight into how many patients discontinue ibrutinib over time because of toxicity. In most trials, this incidence ranges from 10% to 20%. This low long-term rate might reflect the fact that patients who do not tolerate treatment will have discontinued it before they would be eligible for long-term follow-up. However, it is encouraging to see that no unexpected toxicity arises in long-term studies. In fact, the discontinuation rates for AEs are highest in the first year, at 6%, and range from 3% to 6% each year thereafter. The 6-year analysis therefore shows that ibrutinib has no late unexpected toxicities, good long-term benefits, and very good long-term tolerability.

### Disclosure

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