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A SPECIAL MEETING REVIEW EDITION

Highlights in B-Cell Malignancies From the 61st American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 61st ASH Meeting • December 7-10, 2019 • Orlando, Florida

Special Reporting on:

- Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients With Chronic Lymphocytic Leukemia: Extended Follow-Up From the E1912 Trial
- A Randomized Phase 3 Trial of Blinatumomab Vs Chemotherapy as Post-Reinduction Therapy in High and Intermediate Risk First Relapse of B-Acute Lymphoblastic Leukemia in Children and Adolescents/Young Adults Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report From Children's Oncology Group Study AALL1331
- Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results From the MRD Cohort of the Phase 2 CAPTIVATE Study
- Combined Ibrutinib and Venetoclax for Patients With Chronic Lymphocytic Leukemia
- ELEVATE TN: Phase 3 Study of Acalabrutinib Combined With Obinutuzumab (O) or Alone vs O Plus Chlorambucil (Clb) in Patients With Treatment-Naive Chronic Lymphocytic Leukemia
- A Phase 1/2 Study of Umbralisib, Ublituximab, and Venetoclax in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia
- KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study
- Efficacy and Safety of Ibrutinib in Combination With Rituximab as Frontline Treatment for Indolent Clinical Forms of Mantle Cell Lymphoma: Preliminary Results of the Geltamo IMCL-2015 Phase II Trial
- Two Years Rituximab Maintenance Vs Observation After First Line Treatment With Bendamustine Plus Rituximab in Patients With Waldenström's Macroglobulinemia: Results of a Prospective, Randomized, Multicenter Phase 3 Study (the StiL NHL7-2008 MAINTAIN trial)

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. In IMBRUVICA® clinical trials, 3.1% of patients taking IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms 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.

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%).

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LEADING THE WAY WITH A WAVE OF EVIDENCE

IMBRUVICA® is the only BTKi with 10 approvals, across 6 indications, based on 10 pivotal trials[1]

INDICATIONS

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

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

WM
- Waldenström's macroglobulinemia (WM)

cGVHD
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

MCL
- Mantle cell lymphoma (MCL) who have received at least one prior therapy*

MZL
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy*

***Accelerated approval was granted for the MCL and MZL indications based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.**

BTKi=Bruton's tyrosine kinase inhibitor.

Confidence built on 150,000+ patients treated worldwide[2†]

†Across all indications as of September 2019.

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

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)‡, diarrhea (41%), anemia (38%)‡, neutropenia (35%)‡, 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 (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)‡, thrombocytopenia (16%)‡, and pneumonia (14%).

Approximately 7% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)‡, muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%)‡, and pneumonia (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (10%)‡, sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

‡Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines 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 brief summary on the following pages.

References: 1. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC. 2019.
2. Data on file, REF-13821. Pharmacyclics LLC.

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

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)
IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information].*

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.

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information].* Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. In IMBRUVICA clinical trials, 3.1% of patients taking IMBRUVICA without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms 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].*

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.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	8[†]
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	5†
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

† Includes one event with a fatal outcome.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Treatment-emergent Grade 4 thrombocytopenia (6%) and neutropenia (13%) occurred in patients.

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

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) ≤ 30 mL/min, AST or ALT ≥ 2.5 x ULN (upper limit of normal), or total bilirubin ≥ 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 (≥ 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 ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

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Table 3: Non-Hematologic Adverse Reactions in ≥ 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
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†
Vascular disorders	Hypertension	16	8

†One patient death due to histiocytic sarcoma.

Table 4: 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 5 and 6 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 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

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
Body System Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
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
General disorders and administration site conditions				
Pyrexia	24	2	15	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 (continued)

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations				
Upper respiratory tract infection	16	1	11	2†
Pneumonia*	15	12†	13	10†
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
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.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† 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 6: 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 7 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 7: 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 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0

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Table 7: 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 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Eye disorders				
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
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
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

HELIOS: Adverse reactions described below in Table 8 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 8: 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 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	56†
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2†	9	1
Hypertension*	11	5	5	2

Table 8: 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 (continued)

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
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%
† 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 9 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 9: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE

Body System Adverse Reaction§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal Disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	27	1	12	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	25	2	58	8
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and Infestations				
Pneumonia*	16	9	9	4†
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

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Table 9: 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§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Metabolism and Nutrition Disorders				
Hyperuricemia	13	1	0	0
Cardiac Disorders				
Atrial Fibrillation	12	5	0	0
General Disorders and Administration Site Conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

§ 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
† Includes one event with a fatal outcome.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in three single-arm open-label clinical trials (Study 1118, Study 1121, and INNOVATE monotherapy arm) and one randomized controlled trial (INNOVATE) in patients with WM or MZL, including a total n=307 patients overall and n=232 patients exposed to IMBRUVICA. Study 1118 included 63 patients with previously treated WM who received single agent IMBRUVICA. Study 1121 included 63 patients with previously treated MZL who received single agent IMBRUVICA. INNOVATE included 150 patients with treatment naïve or previously treated WM who received IMBRUVICA or placebo in combination with rituximab. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received IMBRUVICA.

The most commonly occurring adverse reactions in Studies 1118, 1121, and INNOVATE (≥ 20%) were thrombocytopenia, diarrhea, bruising, neutropenia, musculoskeletal pain, hemorrhage, anemia, rash, fatigue, and nausea.

Seven percent of patients receiving IMBRUVICA across Studies 1118, 1121, and INNOVATE discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were atrial fibrillation, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

Study 1118 and INNOVATE Monotherapy Arm: Adverse reactions and laboratory abnormalities described below in Tables 10 and 11 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 10: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0

Table 10: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 11: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

	Percent of Patients (N=94)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	38	11
Neutrophils Decreased	43	16
Hemoglobin Decreased	21	6

Treatment-emergent Grade 4 thrombocytopenia (4%) and neutropenia (7%) occurred in patients.

INNOVATE: Adverse reactions described below in Table 12 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 12: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	4†
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0

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Table 12: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE (continued)

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and Lymphatic System Disorders				
Neutropenia*	16	12	11	4
Cardiac Disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	2†
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Treatment-emergent Grade 4 thrombocytopenia (3%) and neutropenia (6%) occurred in patients.

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 15 and 16 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 15: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	14†
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

† Includes 2 events with a fatal outcome.

Table 16: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Treatment-emergent Grade 4 neutropenia occurred in 2% of patients.

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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 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), onychoclasis, 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. 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 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

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 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

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]*.

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

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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]*.
- *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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Patent *http://www.imbruvica.com*

PRC-05657

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients With Chronic Lymphocytic Leukemia: Extended Follow-Up From the E1912 Trial

Chemoimmunotherapy consisting of fludarabine, cyclophosphamide, and rituximab (FCR) remains a key first-line treatment for patients with chronic lymphocytic leukemia (CLL). This regimen is particularly effective for patients with mutations in the immunoglobulin heavy chain variable (*IGHV*) region.[1] The phase 3 Eastern Cooperative Oncology Group (ECOG) 1912 trial (E1912) compared ibrutinib plus rituximab vs FCR in patients with treatment-naive CLL.[2,3] Eligible patients had an ECOG performance status of 0 to 2, were ages 70 years or younger, and did not have the 17p deletion (del[17p]) according to fluorescence in situ hybridization. After stratification by age, disease stage, performance status, and deletion 11q23 status, patients were randomly assigned 2:1 to receive ibrutinib plus rituximab vs FCR. For the first 28-day cycle, patients in the ibrutinib/rituximab arm received ibrutinib monotherapy (420 mg daily). For cycles 2 to 6, these patients also received rituximab (50 mg/m^2 on day 1 of cycle 2, 325 mg/m^2 on day 2 of cycle 2, and 500 mg/m^2 on day 1 of cycles 3-7). Patients then received daily ibrutinib monotherapy starting with cycle 8 and continued until disease progression. Patients in the control arm received 6 cycles of FCR therapy, consisting of fludarabine (25 mg/m^2, days 1-3) and cyclophosphamide (250 mg/m^2, days 1-3), plus rituximab.

After a median follow-up of 34 months, initial results from 529 patients showed a survival benefit with ibrutinib plus rituximab compared with FCR.[3] The median progression-free survival (PFS) was 89.4% with ibrutinib plus rituximab vs 72.9% with FCR (hazard ratio [HR], 0.35; 95% CI, 0.22-0.56; *P*<.001). Three-year median overall survival (OS) was 98.8% with ibrutinib plus rituximab vs 91.5% with FCR (HR, 0.17; 95% CI, 0.05-0.54; *P*<.001). However, only a small number of deaths had occurred at the time of this report. Subset analysis showed a significant benefit from ibrutinib plus rituximab in patients with unmutated *IGHV*, but not in those with mutated *IGHV*.

Dr Tait Shanafelt presented an extended follow-up analysis from the E1912 trial.[2] The median duration of follow-up was 48 months. This second analysis focused on ibrutinib tolerability, reasons for discontinuation, impact of *TP53* mutations, and efficacy.[2] The *TP53* mutation was observed in 9% of patients (27/272) in the ibrutinib/

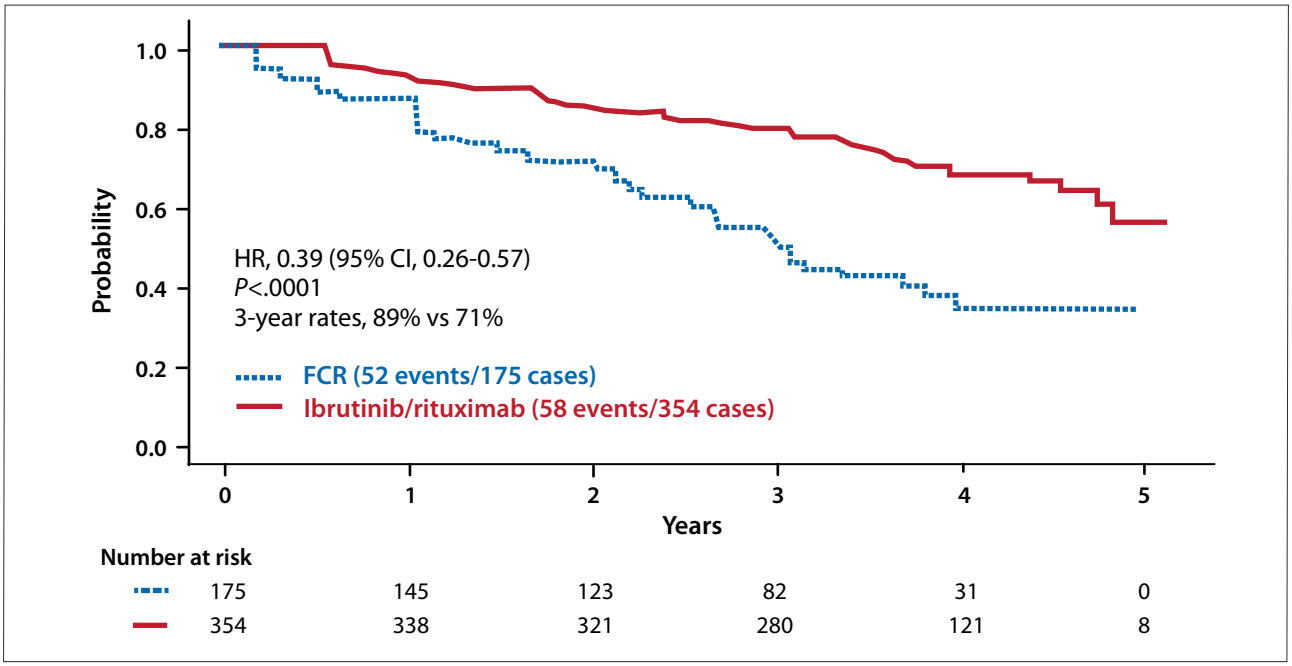

Figure 1. Progression-free survival in an extended follow-up analysis of the phase 3 E1912 trial, which compared ibrutinib plus rituximab vs FCR in patients with treatment-naive chronic lymphocytic leukemia. FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio. Adapted from Shanafelt TD et al. ASH abstract 33. *Blood*. 2019;134(suppl 1).[2]

rituximab arm and 3% of those in the FCR arm (4/134).

Among 354 patients originally assigned to ibrutinib plus rituximab, 257 (73%) remained on ibrutinib monotherapy, with a median time on treatment of 43 months. Among the 95 patients (27%) who discontinued ibrutinib, the median time on treatment was 20.3 months. The most common reasons for treatment discontinuation were adverse events (AEs; 51%) and disease progression or death (24%). Among the 72 patients who discontinued ibrutinib for reasons other than disease progression or death, the median PFS was 22.5 months. Multivariable analysis identified only a higher Cumulative Illness Rating Scale (CIRS) score as a predictor of discontinuation (HR, 1.13 per CIRS unit increase; 95% CI, 1.03-1.23; *P*=.009). The HR for PFS continued to favor ibrutinib plus rituximab over FCR (89% vs 71%; HR, 0.39; 95% CI, 0.26-0.57; *P*<.0001; Figure 1). Among patients with unmutated *IGHV*, PFS was 89% with ibrutinib plus rituximab vs 65% with FCR (HR, 0.28; 95% CI, 0.17-0.48; *P*<.0001; Figure 2). In patients with mutated *IGHV*, PFS was 88% vs 82%, respectively, a difference that was not significant (HR, 0.42; 95% CI, 0.16-1.16; *P*=.086). For the overall study population, 3-year OS was 99% with ibrutinib plus rituximab vs 93% with FCR (HR, 0.34; 95% CI, 0.15-0.79; *P*=.009).

The rate of grade 3 or higher treatment-related AEs was 70% with ibrutinib plus rituximab vs 80% with FCR (odds ratio, 0.56; 95% CI, 0.34-0.90; *P*=.013). The most common grade 3 or higher AEs in the FCR arm included decreased neutrophil count (43% vs 27% with ibrutinib/rituximab), anemia (15.8% vs 4.3%), decreased platelet count (15.8% vs 3.1%), and febrile neutropenia (15.8% vs 2.3%). Patients in the ibrutinib combination arm were more likely to develop hypertension (8.5% vs 1.9% with FCR), cardiac events (5.4% vs 0%), and arthralgia (5.1% vs 0.6%).

The trial investigators concluded that PFS and OS were superior with ibrutinib plus rituximab compared with FCR. At a median follow-up of 48 months, 73% of patients in the ibrutinib/rituximab arm were still receiving treatment. Among the patients who discontinued ibrutinib for reasons other than progressive disease or death, disease did not progress for a median of 23 months after the last dose.

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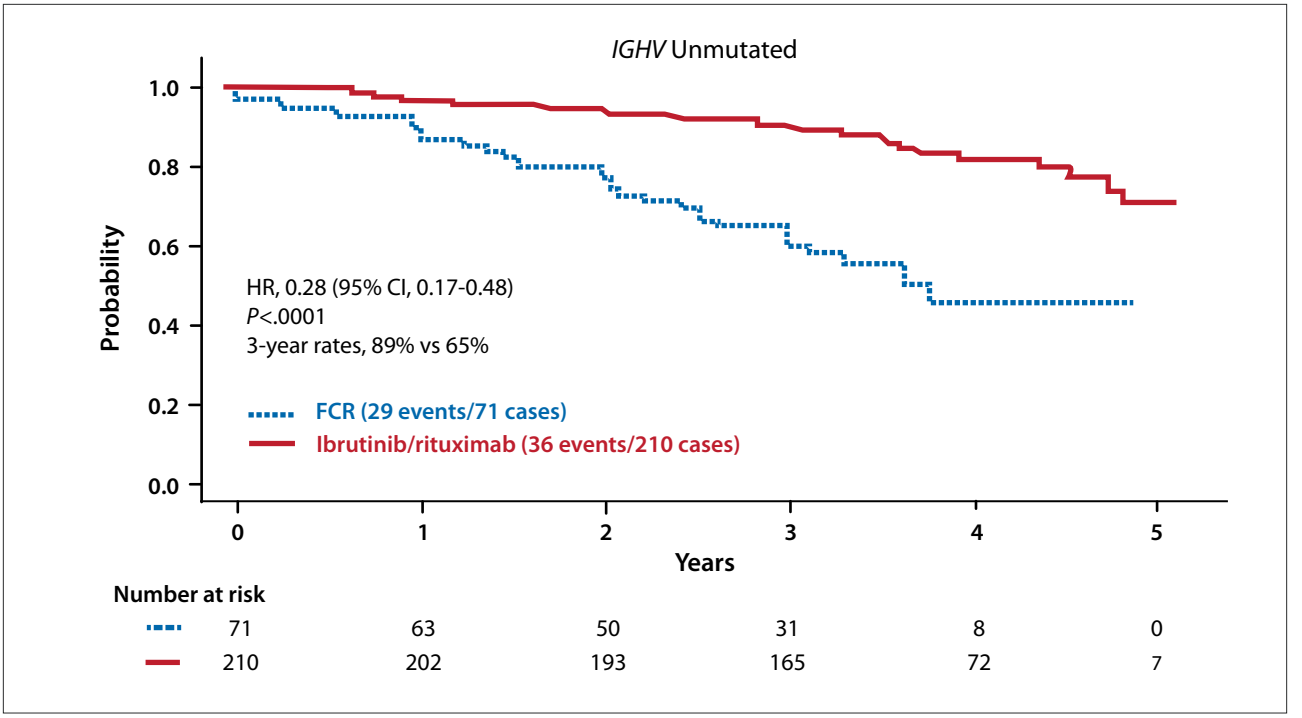

Figure 2. Progression-free survival among *IGHV* unmutated patients in an extended follow-up analysis of the phase 3 E1912 trial, which compared ibrutinib plus rituximab vs FCR in patients with treatment-naive chronic lymphocytic leukemia. FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; *IGHV*, immunoglobulin heavy chain variable. Adapted from Shanafelt TD et al. ASH abstract 33. *Blood*. 2019;134(suppl 1).[2]

A Randomized Phase 3 Trial of Blinatumomab Vs Chemotherapy as Post-Reinduction Therapy in High and Intermediate Risk First Relapse of B-Acute Lymphoblastic Leukemia in Children and Adolescents/Young Adults Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report From Children's Oncology Group Study AALL1331

The phase 3 AALL1331 study (Blinatumomab in Treating Younger Patients With Relapsed B-Cell Acute Lymphoblastic Leukemia) evaluated standard therapy vs blinatumomab in patients ages 1 to 30 years with relapsed disease after first-line treatment for B-cell acute lymphoblastic leukemia.[1] All patients received initial treatment with block 1 induction chemotherapy that contained mitoxantrone.[2] Patients with less than 25% marrow blasts were stratified by risk factors and then randomly assigned into the 2 arms. Patients in the control arm received block 2 and block 3 induction chemotherapy.[2] Patients in the experimental arm received 2 cycles of blinatumomab (15 μg/m^2 daily) for 28 days per cycle, followed by 7 days off. During cycle 1, patients also received dexamethasone (5 mg/m^2). All patients then underwent hematopoietic stem cell transplant. The primary endpoint was disease-free survival. The study assumed enrollment of 110 patients per arm and an increase in 2-year disease-free survival from 45% to 63%, providing an 85% power to detect an HR of 0.58 with a 1-sided α of 0.025. The monitoring committee stopped enrollment into the control arm after a planned interim analysis showed that blinatumomab improved disease-free survival, OS, and clearance of minimal residual disease (MRD).

The study enrolled 103 patients into the control arm and 105 into the experimental arm. The patients' median age was 9 years (range, 1-27 years). After stratification, one-third of patients in each arm had intermediate-risk disease, based on late relapse and high MRD. Two-thirds of patients had high-risk disease, as indicated by early relapse. After a median follow-up of 1.4 years, 2-year disease-free survival was 59.3% ± 5.4% in the blinatumomab arm vs 41.0% ± 6.2% in the control arm (*P*=.05). Two-year OS was 79.4% ± 4.5% with blinatumomab vs 59.2% ± 6.0% with chemotherapy (*P*=.005; Figure 3). After block 1 chemotherapy, the rate of undetectable MRD—

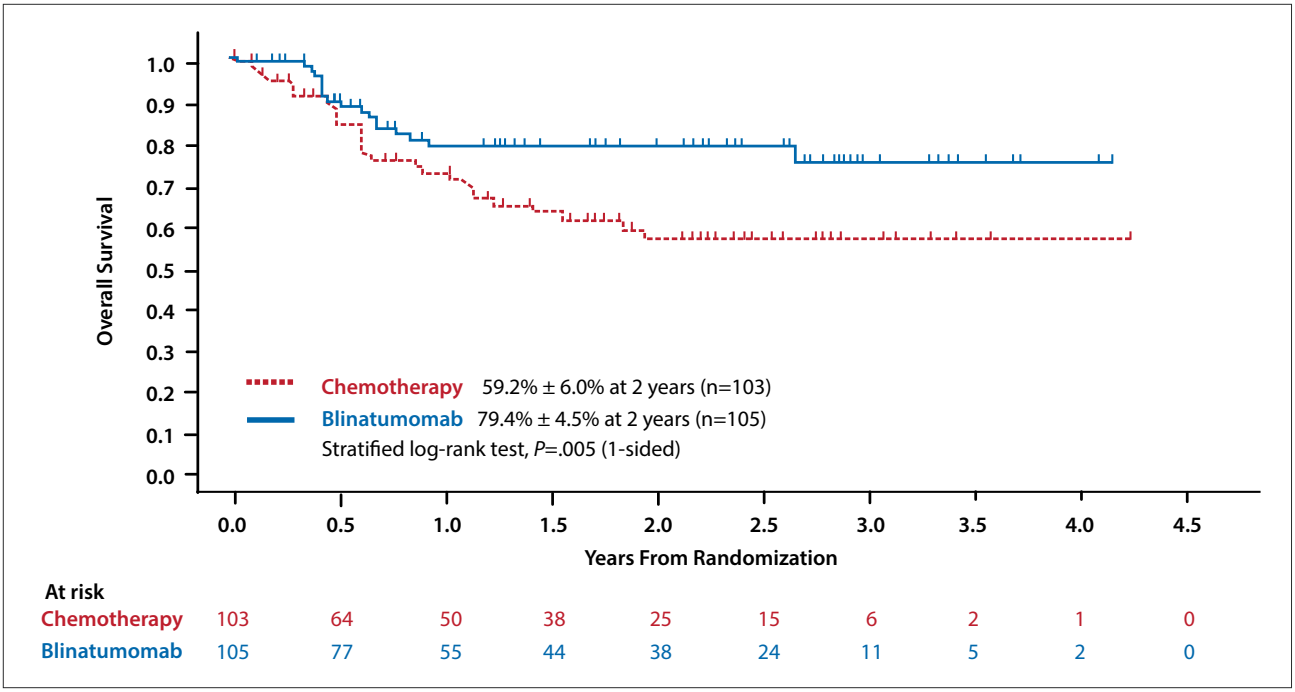

Figure 3. Overall survival in the phase 3 AALL1331 study, which evaluated standard therapy vs blinatumomab in patients ages 1 to 30 years who had relapsed after first-line treatment for B-cell acute lymphoblastic leukemia. ALL1331, Blinatumomab in Treating Younger Patients With Relapsed B-Cell Acute Lymphoblastic Leukemia. Adapted from Brown PA et al. ASH abstract LBA1. *Blood*. 2019;134(suppl 1).[1]

defined as no more than 0.01% malignant cells—was 18% in the blinatumomab arm vs 22% in the control arm (*P*=.65). After the second cycle, the rate of undetectable MRD was 76% with blinatumomab vs 29% with the control treatment (*P*<.0001). This trend was also observed after the third treatment cycle, with rates of 66% vs 33%, respectively (*P*<.0001). A higher proportion of patients in the blinatumomab arm proceeded to transplant (73% vs 45%; *P*<.0001), which likely contributed to the improved OS in this arm.

After induction therapy, 4 patients died; all were in the control arm and all died from infections. Rates of febrile neutropenia, infection, sepsis, and mucositis were all significantly higher after block 2 induction vs cycle 1 of blinatumomab (*P*<.001). After block 3 chemotherapy and cycle 2 of blinatumomab, rates of febrile neutropenia, infection, and sepsis were again significantly higher in the control arm (*P*<.001). Rates of mucositis were similar (*P*=.16). The most common AE associated with blinatumomab was any-grade cytokine-release syndrome, which occurred in 22% of patients after cycle 1 but dropped to 1% after cycle 2. Neurotoxicity occurred in 18% after cycle 1 and 11% after cycle 2.

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

Ibrutinib and venetoclax have complementary mechanisms of action and have demonstrated synergistic activity in preclinical, ex vivo, and clinical studies.[1,2] The multicenter, phase 2 CAPTIVATE study (Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) evaluated ibrutinib plus venetoclax in patients with previously untreated CLL or small lymphocytic lymphoma (SLL).[3] Eligible patients had active disease requiring treatment and were younger than 70 years. They had an ECOG performance status of 0 or 1. Patients first received 3 cycles of daily ibrutinib (420 mg/day), followed by 12 cycles of ibrutinib plus venetoclax (escalated to 400 mg/day). Further treatment was based on MRD status. Patients with undetectable MRD ($<10^{-4}$ by 8-color flow cytometry) were randomly assigned to receive either ibrutinib monotherapy or placebo. Patients with detectable MRD were randomly assigned to receive open-label ibrutinib or ibrutinib plus venetoclax.

The MRD cohort included 164 patients, with a median age of 58 years (range, 28-69 years). Thirty-two percent of patients had Rai stage III/IV disease. Genetic abnormalities included unmutated *IGHV* in 59%, del(17p)/*TP53* mutation in 20%, complex karyotype in 19%, and del(11q) in 17%. Thirty-two percent of patients had a lymph node with a diameter of at least 5 cm, and 3% had a nodal diameter of at least 10 cm. Cytopenias were observed in 36% of patients. At baseline, the risk of tumor lysis syndrome was high in 24% and medium in 63%. After 3 cycles of ibrutinib lead-in, the risk of tumor lysis syndrome was high in 2%, medium in 65%, and low in 30%. In patients with a high risk of tumor lysis syndrome at baseline, 90% shifted to medium or low risk after ibrutinib lead-in therapy, and 74% were not hospitalized after initiation of venetoclax.

Ninety percent of patients completed all 12 cycles of ibrutinib plus venetoclax. The median duration of treatment was 14.7 months for ibrutinib (range, 0.5-19.9 months) and

ABSTRACT SUMMARY Three-Year Update of the Phase II ABT-199 (Venetoclax) and Ibrutinib in Mantle Cell Lymphoma (AIM) Study

An investigator-initiated, open-label, single-arm phase 2 study evaluated daily ibrutinib (560 mg) and venetoclax (400 mg) in 24 patients with relapsed or refractory mantle cell lymphoma (Abstract 756). The patients' median age was 68 years (range, 47-81 years). They had received a median of 2 lines of prior therapy (range, 1-6). One patient was treatment-naive. At week 16, the ORR was 75%, with a 42% CR rate. Undetectable MRD in the bone marrow, as assessed by flow cytometry, was reported in 67% of patients. The median PFS was 29 months, and the median OS was 32 months. Among 5 patients who achieved an MRD-negative CR, 4 remained progression-free at the time of the report, and 1 patient developed radiologic progression after 7 months. The most common AEs of grade 3 or higher were neutropenia (33%), thrombocytopenia (17%), diarrhea (12%), and anemia (12%). Two patients developed treatment-related myelodysplastic syndrome.

12 months for venetoclax (range, 0.8-12.7 months). Among patients who initiated ibrutinib lead-in therapy, 4 discontinued owing to AEs and 1 discontinued after Richter transformation. Among patients who completed lead-in therapy and initiated the combination treatment, 4 discontinued owing to AEs, 1 discontinued owing to disease progression, 1 discontinued based on the investigator's decision, and 1 withdrew. No deaths occurred. The lead-in and combination treatment cycles were completed by 152 patients (93%).

Among patients treated with up to 12 cycles of ibrutinib plus venetoclax, the rate of undetectable MRD was 75% (95% CI, 67%-81%) in the peripheral blood and 72% (95% CI, 64%-79%) in the bone marrow. Among patients who achieved undetectable MRD in the peripheral blood at cycle 16 and who had matched bone marrow samples, 93% also had undetectable MRD in the bone marrow. In the intention-to-treat population of 164 patients, rates of undetectable MRD were 74% in the peripheral blood and 68% in the bone marrow. The proportion of patients with undetectable MRD ($<10^{-4}$) in the peripheral blood increased throughout the 12 cycles of 2-drug therapy, from 57% after 6 cycles to 73% after 12 cycles (Figure 4). Undetectable MRD was observed across all subgroups, including those based on age, Rai disease stage, bulky disease, cytogenetics, del(17p) or *TP53* mutation, *IGHV* status, and complex karyotype.

The most common AE arising during the single-agent ibrutinib lead-in period was grade 1 diarrhea. The combination of ibrutinib plus venetoclax was generally well tolerated. The most common grade 3/4 AEs overall were neutropenia (35%), hypertension (7%), thrombocytopenia (5%), and diarrhea (5%). There were no cases of clinical tumor lysis syndrome. Laboratory tumor lysis syndrome was reported as an AE in 3 patients (with 1 case meeting the Howard criteria). Grade 3/4 AEs were most common during the first 3 cycles of combination treatment (39%) and decreased during subsequent cycles (15% during the final 3-4 treatment cycles). AEs that required discontinuation of treatment (ibrutinib during the lead-in period or both ibrutinib and venetoclax during combination treatment) were reported in 5% of patients.

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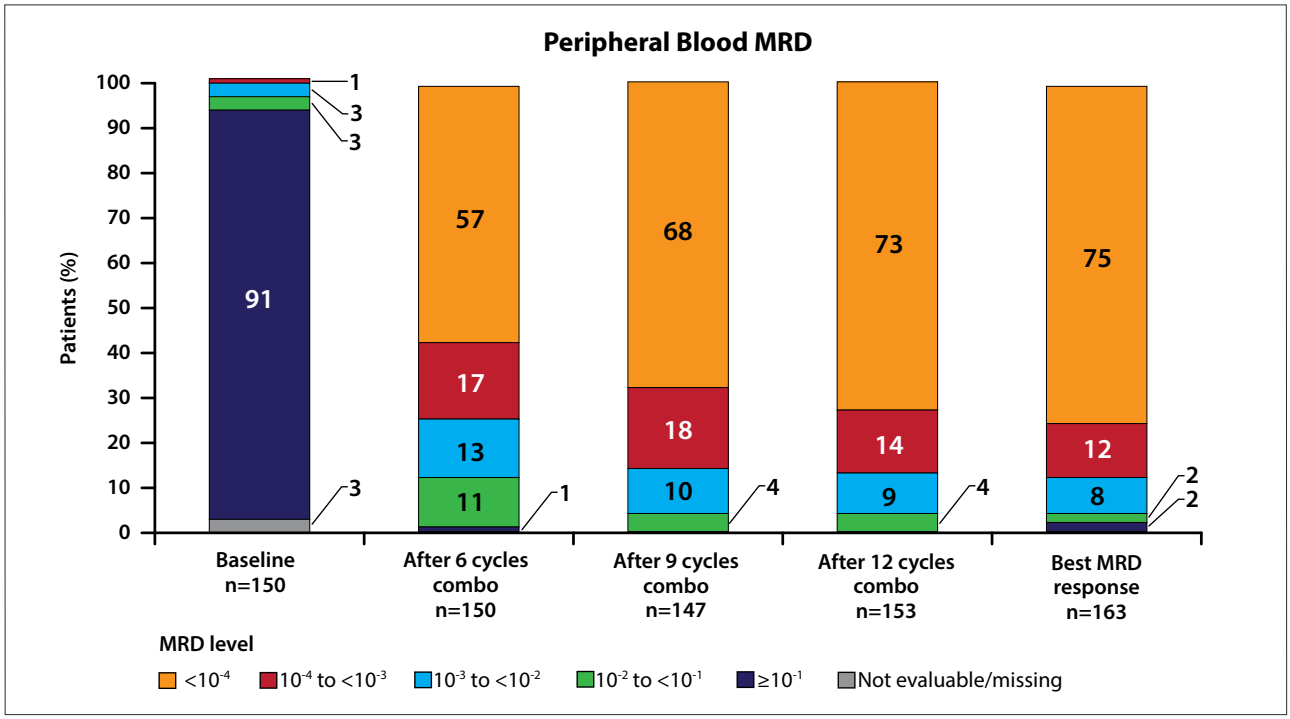

Figure 4. Levels of MRD in the peripheral blood over time among patients in the phase 2 CAPTIVATE trial, which evaluated ibrutinib plus venetoclax in patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma. CAPTIVATE, Ibrutinib Plus Venetoclax in Subjects With Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; combo, combination; MRD, minimal residual disease. Adapted from Tam CS et al. ASH abstract 35. *Blood.* 2019;134(suppl 1).[3]

Combined Ibrutinib and Venetoclax for Patients With Chronic Lymphocytic Leukemia

The combination of ibrutinib plus venetoclax for the treatment of patients with CLL or SLL was evaluated in 2 investigator-initiated phase 2 studies, one in treatment-naive patients and the other in patients with relapsed/refractory disease.[1,2] The study in the treatment-naive setting required patients to have at least 1 risk factor: del(17p) or mutated *TP53*, del(11q), unmutated *IGHV*, or older age (≥65 years).[1] Patients first received 3 cycles of ibrutinib (420 mg daily) as lead-in therapy, in cycles of 28 days. Starting with the fourth treatment cycle, venetoclax was included at a starting dose of 20 mg daily, with escalation to 400 mg daily. Patients received 24 cycles of combination therapy. Patients with detectable MRD after completing combination therapy continued to receive ibrutinib monotherapy until disease progression. Response was evaluated based on 2008 International Workshop CLL criteria.[3] Bone marrow MRD was assessed by flow cytometry with a sensitivity of 10^{-4}.

Among 80 enrolled patients, 75 (94%) initiated combination therapy with ibrutinib plus venetoclax. The median age of enrolled patients was 65 years (range, 26-83 years), and 71% were male. Eighty-three percent of patients had unmutated *IGHV*. Fluorescence in situ hybridization identified del(11q) in 25%, del(13q) in 24%, trisomy 12 in 21%, and del(17p) in 18%. Among the 49 patients who completed study therapy, the rate of undetectable MRD in the bone marrow was 75% (Figure 5). The rate of undetectable MRD at 12 months was similar across all subgroups. Among the patients with detectable MRD at 12 months, improvement continued through month 24.

Grade 3/4 neutropenia occurred in 51% of patients. Ten percent of patients developed atrial fibrillation of grade 3 or higher. Infections of grade 3 or higher were reported in 19%. The dose of ibrutinib was reduced in 52%, and the dose of venetoclax was reduced in 29%.

A related investigator-initiated, phase 2 study evaluated patients with relapsed or refractory CLL/SLL requiring treatment.[2,3] Patients in this study received 3 cycles of ibrutinib monotherapy, followed by 24 cycles of ibrutinib plus venetoclax. MRD-positive patients received subsequent therapy with daily ibrutinib monotherapy. Bone marrow MRD was assessed by flow cytometry with a sensitivity of 10^{-4}. Among 79 enrolled CLL patients,

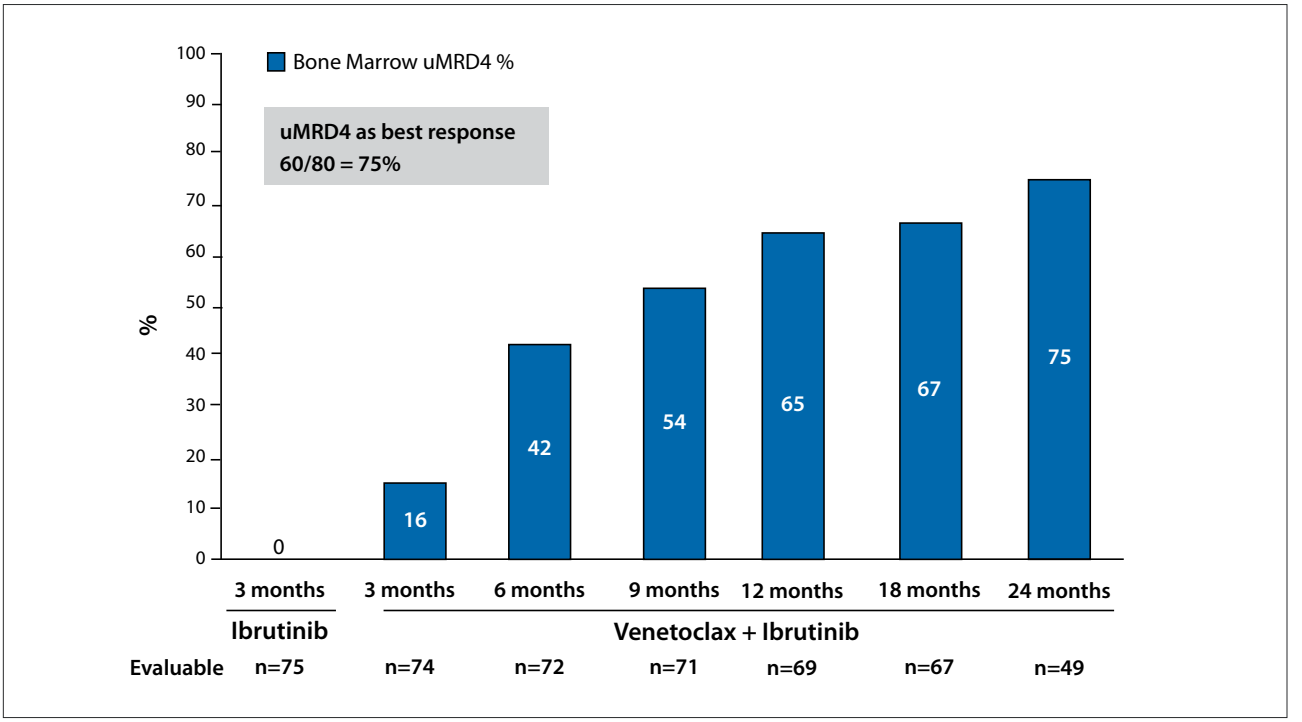

Figure 5. Levels of undetectable MRD (<10^{-4}) in the bone marrow among patients with treatment-naive chronic lymphocytic leukemia who received ibrutinib and venetoclax in a phase 2 trial. MRD, minimal residual disease. Adapted from Jain N et al. ASH abstract 34. *Blood*. 2019;134(suppl 1).[1]

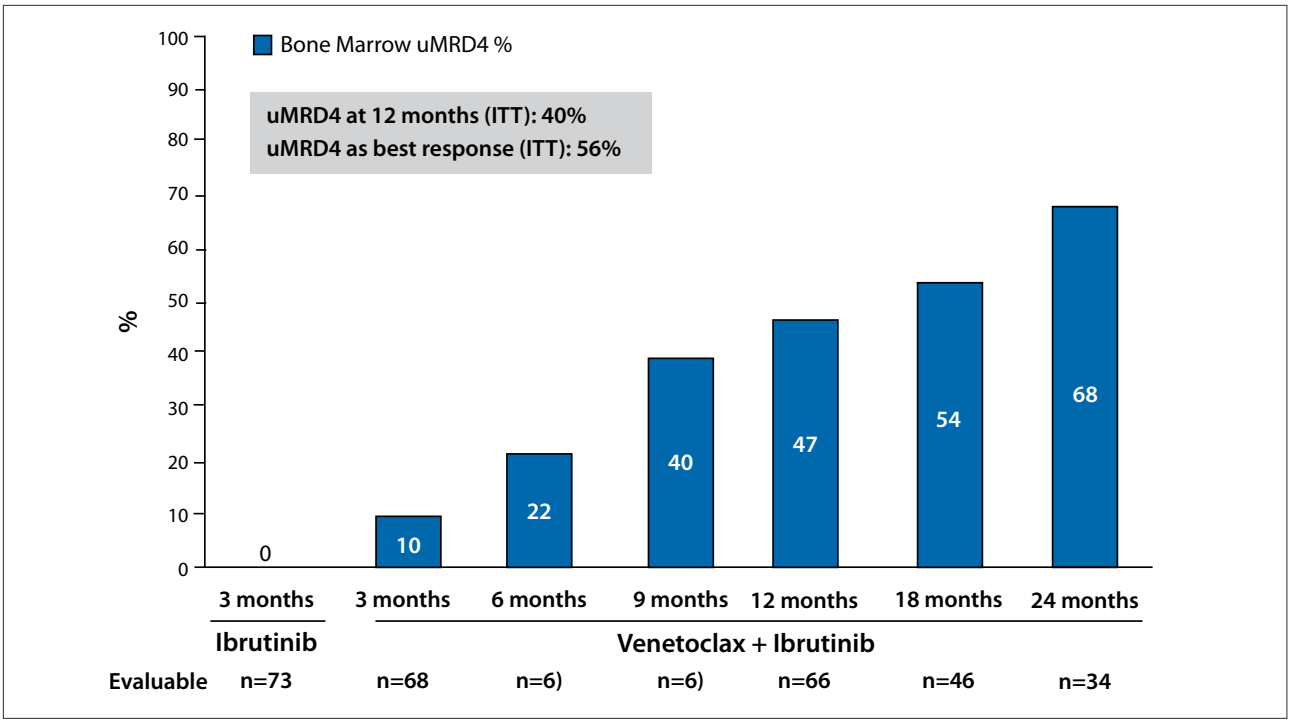

Figure 6. Levels of undetectable MRD ($<10^{-4}$) in the bone marrow among patients with relapsed/refractory chronic lymphocytic leukemia treated with ibrutinib and venetoclax in the intention-to-treat population in a phase 2 trial. MRD, minimal residual disease. Adapted from Jain N et al. ASH abstract 359. *Blood.* 2019;134(suppl 1).[2]

74 initiated combination treatment. Among the enrolled patients, the median age was 61 years (range, 32-79 years), and 72% were male. The median number of prior therapies was 1 (range, 1-4). Eighty-five percent of patients had unmutated *IGHV*. Fluorescence in situ hybridization identified del(11q) in 32%, del(17p) in 25%, del(13q) in 24%, and trisomy 12 in 13%. The median follow-up was 27 months.

In the intention-to-treat population, the rate of undetectable MRD in the bone marrow was 40% after 12 months of treatment (ibrutinib monotherapy followed by the combination). The response rates improved with ongoing treatment (Figure 6).

Among the 16 patients (20%) who left the study, 5 did so during ibrutinib monotherapy, 7 during combination therapy, and 4 during or after combination therapy. AEs of interest included grade 3/4 neutropenia (43%), atrial fibrillation (8%), and grade 3/4 thrombocytopenia (1%). The dose of ibrutinib was reduced in 57%, and the dose of venetoclax was reduced in 35%.

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ELEVATE TN: Phase 3 Study of Acalabrutinib Combined With Obinutuzumab (O) or Alone vs O Plus Chlorambucil (Clb) in Patients With Treatment-Naive Chronic Lymphocytic Leukemia

The phase 3 ELEVATE TN study (Study of Obinutuzumab + Chlorambucil, Acalabrutinib [ACP-196] + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL) evaluated acalabrutinib plus obinutuzumab, chlorambucil plus obinutuzumab, and acalabrutinib monotherapy in patients with previously untreated CLL.[1] The study enrolled patients ages 65 years or older, as well as younger patients with a CIRS score higher than 6 or creatinine clearance below 70 mL/min. The patients were randomly assigned into the 3 treatment arms. Acalabrutinib (100 mg, twice daily) was administered every day. Obinutuzumab (1000

mg) was given on days 1 and 2 of cycle 1, on days 8 and 15 of cycle 2, and subsequently on day 1 of each 28-day cycle for a total of 6 cycles. Chlorambucil (0.5 mg/kg) was administered on days 1 and 15 of each cycle for 6 cycles. Crossover from the chlorambucil/obinutuzumab arm was allowed after disease progression. Patients were stratified according to presence of the del(17p) mutation, ECOG performance status, and geographic location. The primary endpoint was PFS, as assessed by independent review. An interim analysis was planned after approximately 111 PFS events had occurred in the combination treatment arms or after 24 months.

The trial enrolled 535 patients into the 3 treatment arms. Baseline characteristics were generally well balanced across the 3 arms. The proportion of patients who discontinued treatment was 20.7% in the acalabrutinib/obinutuzumab arm, 20.1% in the acalabrutinib monotherapy arm, and 18.1% in the obinutuzumab/chlorambucil arm. After a median follow-up of 28.3 months, the median PFS was 93% with acalabrutinib plus obinutuzumab vs 47% with chlorambucil plus obinutuzumab (HR, 0.10; 95% CI, 0.06-0.17; *P*<.0001; Figure 7). Acalabrutinib monotherapy also yielded a superior median PFS compared with the chlorambucil combination (HR, 0.20; 95% CI, 0.13-0.30; *P*<.0001). A consistent PFS benefit was seen with acalabrutinib, both alone or combined with obinutuzumab, compared with chlorambucil plus obinutuzumab in subgroups based on age, sex, disease stage, and ECOG performance status. Treatment with acalabrutinib plus obinutuzumab led to an overall response rate (ORR) of 93.9% (95% CI, 89.3%-96.5%), including a complete response (CR) rate of 13%, and a CR with incomplete bone marrow recovery rate of 1% (*P*=.0001 vs chlorambucil plus obinutuzumab). With acalabrutinib monotherapy, the ORR was 85.5% (95% CI, 79.6%-89.9%; *P*<.0763 vs chlorambucil plus obinutuzumab). One patient (1%) had a CR after acalabrutinib monotherapy. The ORR with the chlorambucil combination was 78.5% (95% CI, 71.6%-89.9%) and included a CR rate of 5%. The median OS was not significantly different for acalabrutinib plus obinutuzumab (*P*=.0577) or for acalabrutinib monotherapy (*P*=.1556) vs chlorambucil plus obinutuzumab.

Serious AEs were reported in 38.8% of the acalabrutinib combination arm, 31.8% of the acalabrutinib monotherapy arm, and 21.9% of the chlorambucil/obinutuzumab arm. AEs of grade 3 or higher were observed in 70.2%, 49.7%, and 69.8% of patients, respectively. Deaths occurred in 2.8%, 3.9%, and 7.1%.

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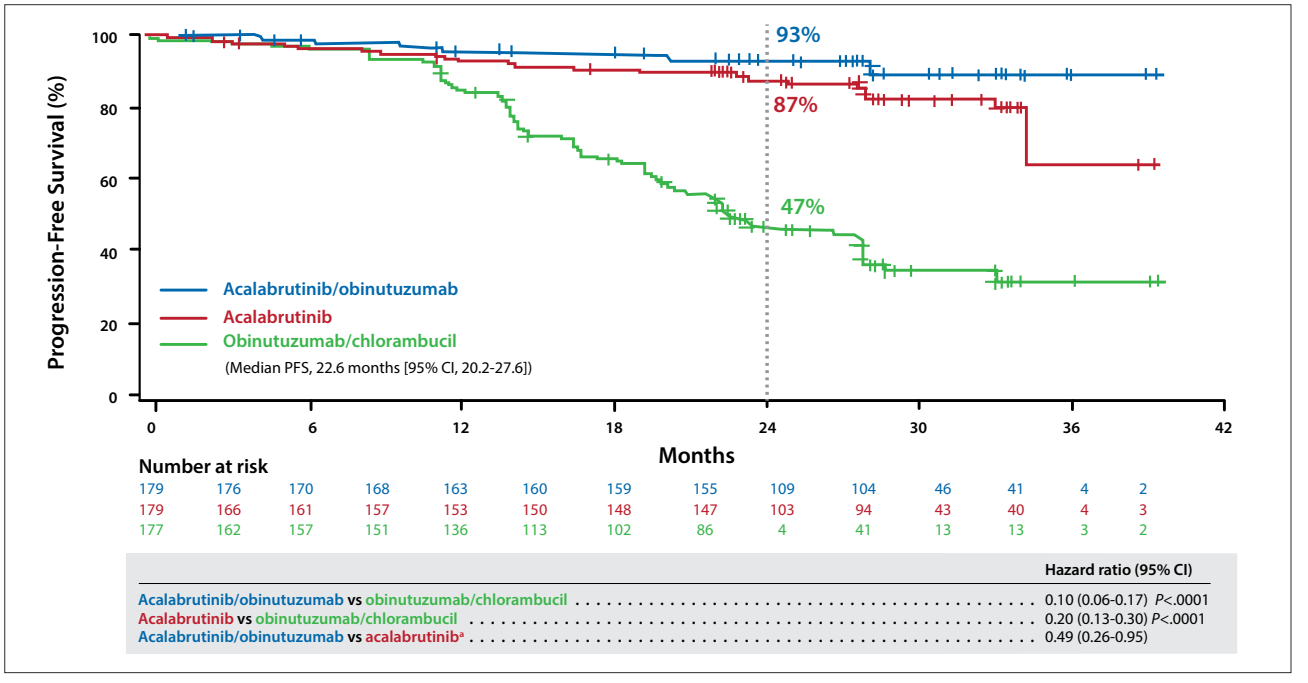

Figure 7. Progression-free survival in an interim analysis of the phase 3 ELEVATE TN study, which evaluated acalabrutinib plus obinutuzumab, chlorambucil plus obinutuzumab, and acalabrutinib monotherapy in patients with previously untreated chronic lymphocytic leukemia. [a]Post hoc analysis. ELEVATE TN, Study of Obinutuzumab + Chlorambucil, Acalabrutinib (ACP-196) + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL; PFS, progression-free survival. Adapted from Sharman JP. ASH abstract 31. *Blood.* 2019;134(suppl 1).[1]

A Phase 1/2 Study of Umbralisib, Ublituximab, and Venetoclax in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia

A phase 1/2 trial evaluated the safety and efficacy of umbralisib, ublituximab, and venetoclax in patients with relapsed or refractory CLL.[1] The treatment consisted of three 28-day cycles of daily umbralisib along with ublituximab administered weekly during cycle 1, then once during cycles 2 and 3, followed by umbralisib and venetoclax for 9 additional cycles. The phase 1 portion tested escalating doses of umbralisib at 600 mg and 800 mg and a fixed dose of ublituximab at 900 mg. Venetoclax was increased in standard fashion to 400 mg during cycle 4. The primary endpoints were safety for phase 1 and CR rate for phase 2. MRD negativity ($<10^{-4}$ by 8-color flow cytometry) was a key secondary endpoint. Patients who were MRD negative after 12 cycles of treatment stopped therapy. Other patients continued treatment with single-agent umbralisib.

At the time of the report, the trial had enrolled 27 patients: 9 in phase 1 and 18 in phase 2. The patients' median age was 63 years, and 67% were male. The median number of prior therapies was 1 (range, 1-5). Among the 21 patients tested, 13 were *IGHV* unmutated. Other high-risk genetic features were the 11q deletion (23%) and the del(17p)/*TP53* mutation (19%).

During the dose-escalation phase, there was 1 dose-limiting toxicity (a lower gastrointestinal bleed), which occurred at the 800-mg dose. The maximum tolerated dose was not reached. The phase 2 doses were 900 mg for ublituximab and 800 mg for umbralisib.

The trial provided efficacy results after cycles 3, 7, and 12. For cycles 3 and 7, the CR rate was not available because CT was used without bone marrow testing. Among the 23 patients who completed the 3-cycle induction phase, the ORR was 87%. All responses were partial. Stable disease was reported in 13%. Among the 13 patients who completed cycle 7, the ORR was 100%, consisting entirely of partial responses. At cycle 12, the ORR was 100% for the 9 patients who completed therapy. Responses were complete in 44% and partial in 56%. Lymph node reduction from baseline reached 87% at cycle 12 (Figure 8).

The study investigators analyzed response according to the method of MRD assessment. At cycle 12, the ORR was 100% in patients who were MRD-negative according to peripheral blood testing and 78% among those tested using bone marrow.

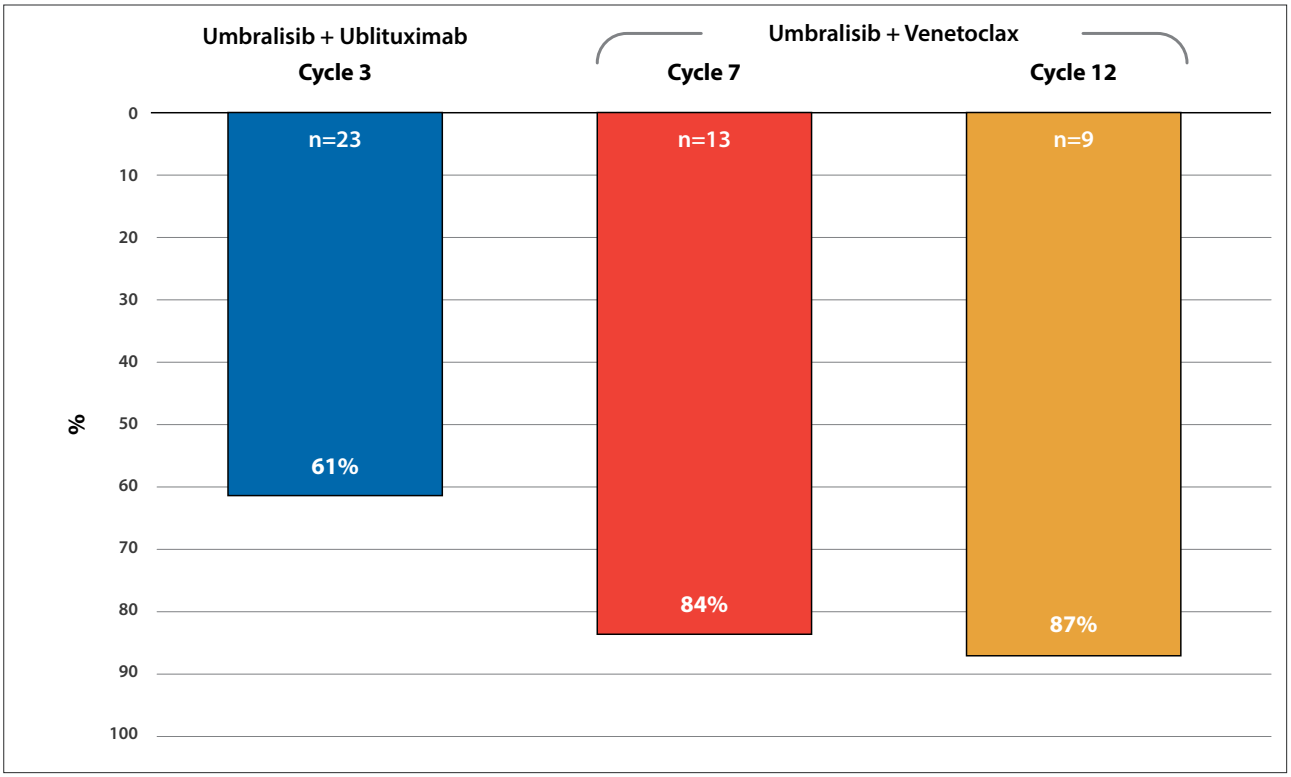

Figure 8. Mean reductions in lymph nodes from baseline in a phase 1/2 study of umbralisib, ublituximab, and venetoclax in patients with relapsed or refractory chronic lymphocytic leukemia. Adapted from Barr PM et al. ASH abstract 360. *Blood*. 2019;134(suppl 1).[1]

Three cycles of debulking with ublituximab and umbralisib reduced the risk of tumor lysis syndrome associated with venetoclax. No patients remained at high risk, and no patients developed clinical or laboratory tumor lysis syndrome during the venetoclax ramp-up period.

The treatment was well tolerated at the phase 2 doses. The most common all-cause AE was infusion reaction, which occurred in 67% of patients. Grade 3/4 infusion reactions were reported in 7%. Other all-cause, all-grade AEs included neutropenia (56%), leukopenia (48%), creatinine increase (48%), thrombocytopenia (48%), and anemia (44%). The most common grade 3/4 AEs were neutropenia (19%) and leukopenia (15%).

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ABSTRACT SUMMARY Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab for First-Line Treatment of *IGHV*-Mutated CLL and Without Del(17p)/Mutated *TP53*

An investigator-initiated phase 2 trial evaluated the combination of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab as first-line treatment in patients with *IGHV*-mutated CLL (Abstract 357). Patients with the *TP53* mutation or del(17p) were excluded from enrollment. All patients initially received 3 cycles of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab. Patients with undetectable bone marrow MRD then received 3 courses of obinutuzumab plus ibrutinib, followed by 6 cycles of ibrutinib monotherapy. All other patients received 9 courses of obinutuzumab plus ibrutinib. Patients with detectable bone marrow MRD after 12 treatment cycles continued with ibrutinib monotherapy. After 3 cycles of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab, 87% of patients had undetectable MRD in the bone marrow. After a median follow-up of 34.2 months, 31 patients (69%) had a CR or incomplete CR, and 44 patients (98%) had undetectable MRD in the bone marrow. Among 41 patients with 1 year of follow-up, all had undetectable bone marrow MRD and discontinued ibrutinib monotherapy per protocol. No clinical relapses were observed. One patient had an MRD relapse. Toxicities were manageable.

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study

KTE-X19 is a chimeric antigen receptor (CAR) T-cell therapy directed at CD19.[1] In addition to a single-chain Fv fragment that binds to CD19, the KTE-19 construct has a CD28 signaling domain and a CD3ζ T-cell activation domain.

The phase 2 ZUMA-2 trial (A Phase 2 Multicenter Study Evaluating Subjects With Relapsed/Refractory Mantle Cell Lymphoma) evaluated KTE-X19 in patients with relapsed or refractory mantle cell lymphoma.[2] Eligible patients had developed disease progression after their most recent treatment or had not achieved a CR or a partial response. The trial enrolled patients who had received up to 5 prior treatments. These prior treatments included chemotherapy with an anthracycline or bendamustine, an anti-CD20 monoclonal antibody, and ibrutinib or acalabrutinib. Patients had at least 1 measurable lesion and an ECOG performance status of 0 or 1. Bridging therapy after leukapheresis was allowed. Conditioning chemotherapy consisted of fludarabine plus cyclophosphamide. The treatment was administered at 2×10^6 KTE-X19 cells/kg, by means of a single infusion. The primary endpoint was independently assessed ORR.

The trial enrolled 74 patients, all of whom underwent leukapheresis. Two patients died from disease progression, and 3 patients were not treated because the manufacture of CAR T cells failed. Sixty-nine patients received conditioning chemotherapy, and 68 patients (92%) received the CAR T-cell infusion. The median time from leukapheresis to delivery of the KTE-X19 CAR T-cell product to the study site was 16 days.

Among the 68 patients who received the CAR T-cell infusion, the median age was 65 years (range, 38-79 years). Eighty-five percent had stage IV mantle cell lymphoma, and 56% had intermediate- or high-risk disease. Bone marrow involvement was observed in 54% of patients, and 69% had a Ki-67 proliferation index of 50% or higher. Patients had received a median of 3 prior therapies (range, 1-5), and 43% had relapsed after autologous stem cell transplant.

After a median follow-up of 12.3 months (range, 7.0-32.3 months), the independently assessed ORR among 60 evaluable patients was 93% (95% CI, 84%-98%). The CR rate was 67%

(95% CI, 53%-78%). The ORR was consistent across most subgroups. The median duration of response was not reached (95% CI, 8.6 months to not estimable; Figure 9). Of the initial 28 patients treated, 43% remained in remission after more than 2 years of follow-up.

Most AEs occurred early, and most cases were reversible. The most common grade 3/4 AEs were hematologic in nature, and included thrombocytopenia (16% grade 3; 69% grade 4), thrombocytopenia (16% grade 3; 35% grade 4), and anemia (50% grade 3; 0% grade 4). Cytokine-release syndrome of grade 3 or 4 occurred in 15% of patients. All cases of cytokine-release syndrome resolved. There were no deaths from cytokine-release syndrome or neurologic events. Neurologic AEs of grade 3 or higher were reported in 31% of patients. Neurologic toxicity resolved in 86% of patients.

ABSTRACT SUMMARY Phase 2 Results of the iR2 Regimen (Ibrutinib, Lenalidomide, and Rituximab) in Patients With Relapsed/Refractory Non–Germinal Center B Cell–Like Diffuse Large B-Cell Lymphoma

An open-label, multicenter, phase 1b/2 study evaluated the combination of ibrutinib, lenalidomide, and rituximab in patients with relapsed or refractory, non–germinal center B-cell–like diffuse large B-cell lymphoma (Abstract 761). Among the 85 patients evaluable for response, the ORR was 47%, including a CR rate of 31%. Tumor size decreased in 68% of patients. After a median time on study of 20 months, 27% of patients remained on treatment. The median duration of response was not reached (range, <1-27 months). Sixteen percent of patients had a CR lasting longer than 1 year. The median PFS was 5 months (range, 3-6 months), and the median OS was 14 months (range, 10 to not estimable). The most common AEs of any grade were diarrhea (53%), neutropenia (44%), and fatigue (43%). The most common grade 3/4 AEs included neutropenia (39%), maculopapular rash (18%), and anemia (13%).

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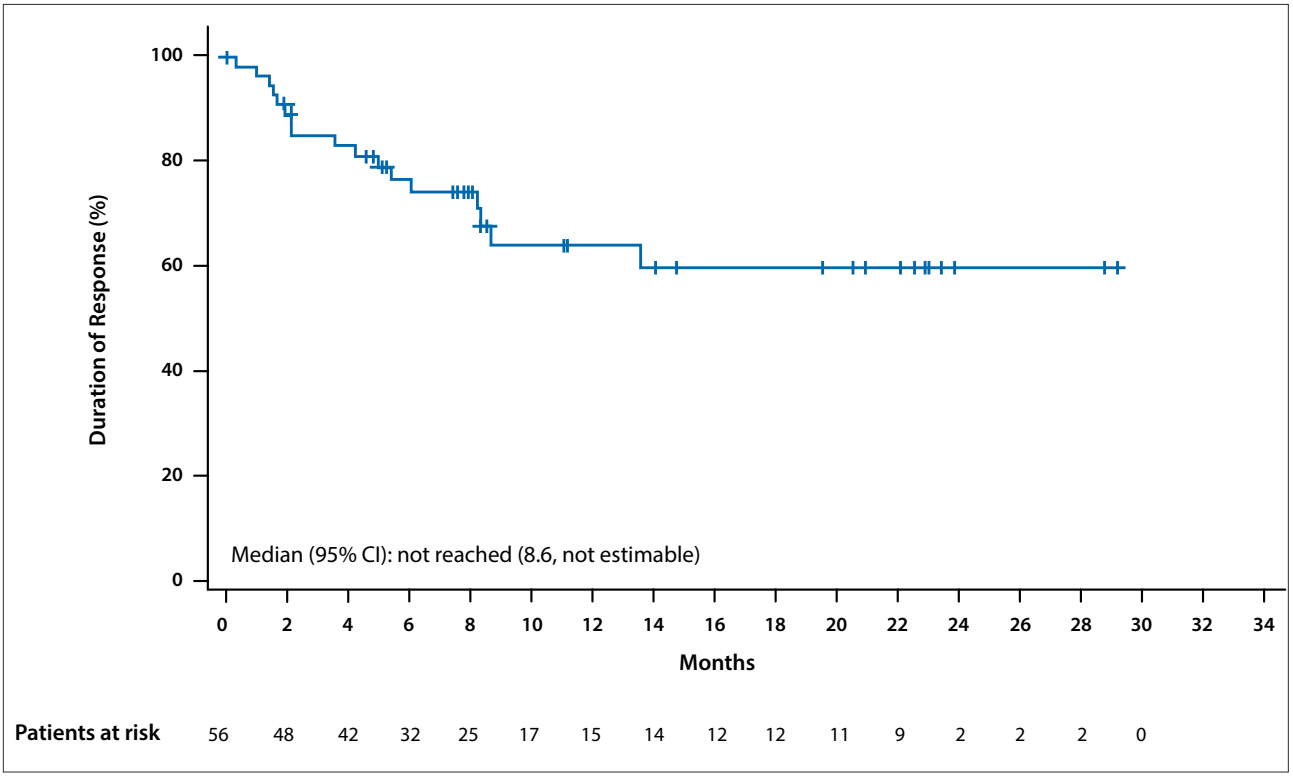

Figure 9. Duration of response in the phase 2 ZUMA-2 trial, which evaluated KTE-X19 in patients with relapsed or refractory mantle cell lymphoma. NE, not estimable; ZUMA-2, A Phase 2 Multicenter Study Evaluating Subjects With Relapsed/Refractory Mantle Cell Lymphoma. Adapted from Wang M et al. ASH abstract 754. *Blood*. 2019;134(suppl 1).[2]

Efficacy and Safety of Ibrutinib in Combination With Rituximab as Frontline Treatment for Indolent Clinical Forms of Mantle Cell Lymphoma: Preliminary Results of the Geltamo IMCL-2015 Phase II Trial

The phase 2 IMCL-2015 study evaluated tailored treatment with ibrutinib plus rituximab in treatment-naive patients with indolent forms of mantle cell lymphoma.[1] The study was conducted at 14 treatment sites in Spain. Patients had indolent mantle cell lymphoma, as defined by the absence of symptoms related to the disease, an ECOG performance status of 0 or 1, stable disease without the need for therapy for at least 3 months, and nonblastoid histology. Patients with blastic or pleomorphic mantle cell lymphoma variants were excluded, as were patients with lymph nodes larger than 3 cm and/or a Ki-67 proliferation index higher than 30%. Patients received ibrutinib (560 mg daily) until disease progression, unacceptable toxicity, or MRD negativity ($<10^{-5}$) lasting at least 6 months after 2 years of therapy. Patients also received rituximab (375 mg/m^2) on days 1, 8, 15, and 22 of cycle 1, and then on day 1 of cycles 3, 5, 7, and 9. The primary endpoint was the CR rate at 12 months by central review.

The 48 enrolled patients had a median age of 65.7 years (range, 41-84 years), and 69% were male. The disease was stage III/IV in 96% of patients, and 77% had intermediate- or high-risk disease. The median follow-up was 23 months (range, 2-41 months).

Among the 35 evaluable patients, the ORR after treatment cycle 12 was 83%, with a CR rate of 77%. Undetectable MRD was reported in both the peripheral blood and bone marrow in 74% of patients overall and in 84% of patients with a CR (Figure 10). Among 22 patients who had completed 24 cycles of treatment, no clinical progression was observed. Thirteen patients with undetectable MRD stopped ibrutinib. One of these patients converted to positive MRD after 30 months, and 6 patients continued to have undetectable MRD after 12 months. Three-year OS was 85% (95% CI, 67%-100%), 3-year PFS was 92% (95% CI, 80%-100%), and 3-year event-free survival was 78% (95% CI, 63%-96%).

The most common AEs consisted of diarrhea (38%), neutropenia (31%), fatigue (31%), upper respiratory infections (25%), and nausea (21%). Grade 3/4 hematologic AEs included neutropenia (16%) and thrombocytopenia (2%).

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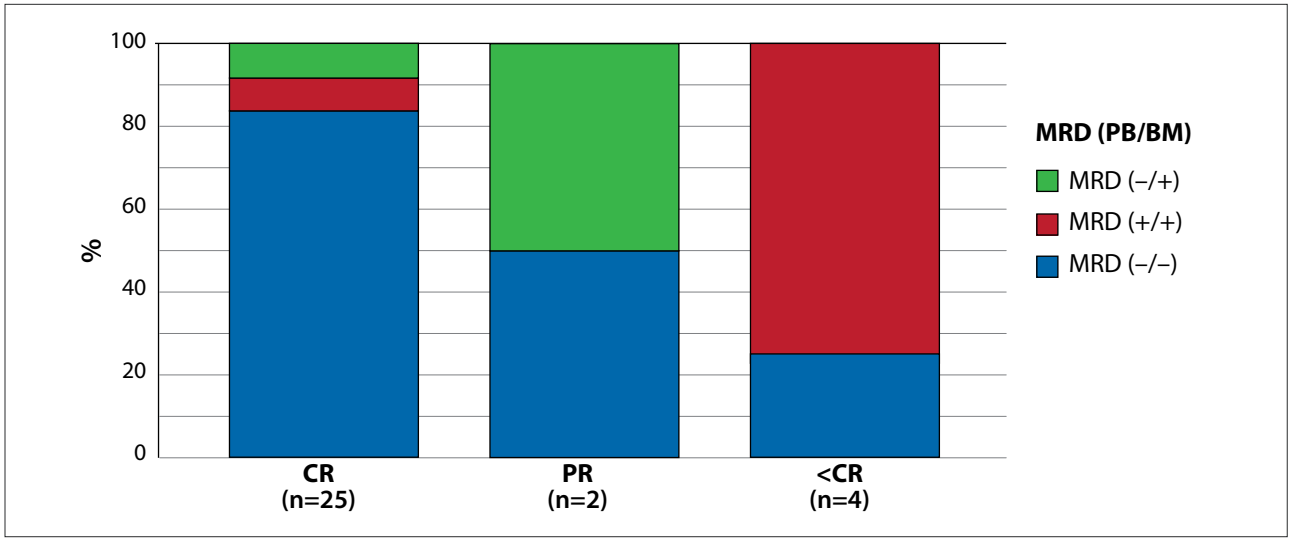

Figure 10. Response according to MRD status in the phase 2 IMCL-2015 study, which evaluated tailored treatment with ibrutinib plus rituximab in treatment-naive patients with indolent forms of mantle cell lymphoma. MRD was assessed with allele-specific oligonucleotide polymerase chain reaction (sensitivity of 10^{-5}) in 22 cases and with next generation-sequencing in 9 cases. MRD was not assessable in 2 patients with a CR. BM, bone marrow; CR, complete response; MRD, minimal residual disease; PB, peripheral blood; PR, partial response. Adapted from Giné E et al. ASH abstract 752. *Blood*. 2019;134(suppl 1).[1]

Two Years Rituximab Maintenance Vs Observation After First Line Treatment With Bendamustine Plus Rituximab in Patients With Waldenström's Macroglobulinemia: Results of a Prospective, Randomized, Multicenter Phase 3 Study (the StiL NHL7-2008 MAINTAIN trial)

The NHL7-2008 MAINTAIN trial (Significance of Duration of Maintenance Therapy With Rituximab in Non-Hodgkin Lymphomas) evaluated 2 years of rituximab maintenance therapy vs observation after induction with bendamustine plus rituximab in 296 patients with Waldenström macroglobulinemia.[1,2] This investigator-initiated, randomized phase 3 study was conducted by the Cooperative Study Group for Indolent Lymphoma at 91 centers throughout Germany and Austria. The primary endpoint was PFS. After a study amendment in 2012, the MAINTAIN trial protocol increased the number of allowed patients from 148 to 290, extended the trial from phase 2 to phase 3, and powered the study to test for improvement in PFS from 60 months to 92 months.

The trial registered 296 patients between April 2009 and October 2017.[1] Eligible patients had treatment-naive Waldenström macroglobulinemia, with stage III/IV disease, an ECOG performance status of 0 to 2, and histology not exceeding 6 months. After induction treatment with bendamustine plus rituximab, 218 patients (74%) had a partial response or better and were randomly assigned into the 2 arms. Patients in the active therapy arm received rituximab every 2 months for 2 years, whereas those in the control arm underwent observation. The median follow-up duration was 77 months for all patients and 80 months for patients randomly assigned to treatment. Among the patients assigned to treatment, the median age was 66 years, and 99% had stage IV disease. Thirty-four percent had B symptoms, and 6% had bulky disease. The disease was considered intermediate risk in 38% of patients and high risk in 39%. Among 266 patients available for response evaluation after induction therapy, the ORR was 93%.

Among 187 patients who received bendamustine plus rituximab as induction therapy, the median PFS was 68.8 months. After the randomized treatment period, secondary primary malignancies were observed in 18% of patients in the rituximab maintenance arm vs 15% in the observation arm. After a median follow-up of 80 months, the median PFS was similar for patients in the 2 treatment arms (HR, 1.21; 95% CI, 0.78-1.89; *P*=.3982). Median OS was also similar (HR, 0.85; 95% CI, 0.46-1.55; *P*=.5962). An exploratory analysis identified a potential benefit for rituximab maintenance in patients older than 65 years (HR, 1.86; 95% CI, 1.03-3.38; *P*=.0355).

Among all patients who were randomly assigned to treatment, the most common grade 3/4 AE was neutropenia, which occurred in 11%. Grade 3/4 leukocytopenia was reported in 7%.

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ABSTRACT SUMMARY Results From a First-in-Human, Proof-of-Concept Phase 1 Trial in Pretreated B-Cell Malignancies for LOXO-305, a Next-Generation, Highly Selective, Non-Covalent BTK Inhibitor

LOXO-305 is a next-generation, highly selective, noncovalent Bruton tyrosine kinase inhibitor that is administered orally. A multicenter phase 1/2 trial of LOXO-305 enrolled patients with advanced B-cell malignancies who had failed or were intolerant to 2 or more lines of prior therapies (Abstract 501). The study enrolled and treated 16 patients with CLL, 8 patients with mantle cell lymphoma, and 4 patients with other B-cell malignancies (Waldenström macroglobulinemia, DLBCL, and marginal zone lymphoma). Among these patients, response was evaluable in 13, 6, and 2, respectively. Across all doses, the ORR was 77% among patients with CLL, 50% among patients with mantle cell lymphoma, and 50% among patients with other B-cell malignancies. A partial response was seen in 62% of patients with CLL and 33% of patients with mantle cell lymphoma. Among patients with CLL, responses deepened over time. The proportion of CLL patients with a partial response increased from 50% at cycle 3 to 88% at cycle 5. There were no dose-limiting toxicities, and the maximum tolerated dose was not reached. No treatment-related grade 3/4 AEs were reported. The investigators noted that the safety and tolerability of LOXO-305 were consistent with the highly selective mechanism of the drug.

Highlights in B-Cell Malignancies From the 61st American Society of Hematology Annual Meeting: Commentary

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Many abstracts presented at the 61st American Society of Hematology (ASH) annual meeting focused on chronic lymphocytic leukemia (CLL), mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), and Waldenström macroglobulinemia. Studies provided updated data for treatments such as ibrutinib, venetoclax, acalabrutinib, and chimeric antigen receptor (CAR) T-cell therapy, as well as novel agents in early development.

Chronic Lymphocytic Leukemia

One of the most important questions for a physician caring for patients with CLL is whether to recommend chemoimmunotherapy or novel agents as frontline therapy. There is a great deal of long-term phase 2 data for fludarabine, cyclophosphamide, and rituximab (FCR) and for ibrutinib.[1-3] Two cooperative group trials were designed to address this question in different populations. A study from the Alliance group evaluated bendamustine plus rituximab, ibrutinib alone, or ibrutinib plus rituximab in patients with previously untreated CLL who were older than 65 years.[4] The Eastern Cooperative Oncology Group (ECOG) 1912 trial compared FCR vs ibrutinib and rituximab in patients younger than 70 years.[5] The initial results of both studies were presented at the 60th ASH meeting and demonstrated the superiority of ibrutinib-based therapy over chemoimmunotherapy.[6,7] One aspect of these data was how early the curves on Kaplan–Meier plots separated and demonstrated a difference. (The median follow-up was 38 months for the Alliance trial and 33 months for the ECOG study.)

Dr Tait Shanafelt and colleagues presented updated results from the ECOG 1912 study.[8] With a median follow-up of 48 months, Dr Shanafelt confirmed the benefits previously seen with ibrutinib plus rituximab compared with FCR in patients with CLL who are younger than 70 years.[8] The 3-year rate of progression-free survival (PFS) was 89% with ibrutinib plus rituximab vs 71% with FCR (95% CI, 0.26-0.57; P<.0001). The PFS benefit was seen primarily in patients without the immunoglobulin heavy chain variable (*IGHV*) mutation, likely because patients with the mutation did well with both treatments. These data also confirmed the previously seen benefit in overall survival for ibrutinib plus rituximab compared with FCR. Only 7% of patients treated with ibrutinib progressed during therapy. These data further support the superiority of ibrutinib-based therapy over chemoimmunotherapy in patients younger than 70 years.

The next logical progression in the treatment paradigm for patients with CLL is the use of combinations of novel agents. It is hoped that utilization of agents with non-overlapping toxicities and synergistic efficacy will achieve deeper and more prolonged responses. Two phase 2 trials investigating the combination of ibrutinib plus venetoclax have been undertaken.[9,10] The first trial, conducted at MD Anderson Cancer Center, investigated ibrutinib plus venetoclax for 24 cycles in treatment-naive and previously treated patients with CLL.[9] With a median follow-up of 27 months for 80 patients in the treatment-naive cohort, 14 patients discontinued therapy for various reasons. Only 2 patients progressed while receiving therapy, both with Richter's transformations. In 75% of patients, minimal residual disease (MRD) was undetectable in the bone marrow after 24 months of combined therapy. Dr Nitin Jain and colleagues presented the results from the relapsed/refractory cohort of the trial.[9] With a median follow-up of 27 months, MRD was undetectable in 56% of patients. Of note, all patients who remained MRD-detectable were allowed to continue single-agent ibrutinib.

The second study is the international CAPTIVATE trial, which investigated 12 cycles of ibrutinib plus venetoclax combination therapy in patients with treatment-naive CLL.[10] The study divided patients into 2 cohorts. The first cohort (known as the MRD cohort) randomly assigned MRD-negative patients to either placebo or ibrutinib and MRD-positive patients to ibrutinib or ibrutinib plus venetoclax. The second cohort (known as the fixed-duration cohort) treated all patients with 12 cycles of combination therapy and then discontinued therapy. At the ASH meeting, Dr Constantine S. Tam reported on the results of the 12 cycles of combination therapy from the MRD cohort of the CAPTIVATE trial.[10] Among 164 patients, including 20% with either deletion 17p or the

TP53 mutation, MRD negativity was achieved in the peripheral blood in 75% and in the bone marrow in 72%.

Both studies utilized a strategy of administering 3 months of treatment with ibrutinib alone to debulk patients prior to initiation of venetoclax, in order to reduce the risk for tumor lysis syndrome.[9,10] In the CAPTIVATE study, the risk of tumor lysis syndrome at enrollment was high, at 24%. This rate was reduced to 2% after 3 cycles of ibrutinib.[10]

The data from these studies are striking for the similar rates of MRD negativity in the bone marrow (75% and 72%), even with different durations of combination therapy. In Dr Jain's data, the MRD negativity rate in the bone marrow after 12 months of combination therapy was 65%.[9] It will be important to determine the best duration of treatment to ensure we are not denying patients therapeutic benefit. The CAPTIVATE study will provide important insight into this issue when the data mature.[10] Regardless, this combination is highly effective, and patients will continue to derive benefit from single-agent ibrutinib.

The ELEVATE TN trial investigated obinutuzumab plus chlorambucil vs obinutuzumab plus acalabrutinib vs acalabrutinib alone. This trial led to the US Food and Drug Administration approval of acalabrutinib for the treatment of patients with CLL.[11] The ELEVATE TN trial randomly assigned 535 patients with treatment-naive CLL to one of the above treatment arms. Patients could be older than 65 years or younger than 65 years with a Cumulative Illness Rating Scale (CIRS) score higher than 6 or a creatinine clearance less than 70 mL/min. After a median follow-up of 28.3 months, the overall response rates (ORRs) were 78.5% with obinutuzumab plus chlorambucil, 93.9% with obinutuzumab plus acalabrutinib, and 85.5% with acalabrutinib. The 2-year PFS was 93% with acalabrutinib plus obinutuzumab (P<.0001 vs obinutuzumab plus chlorambucil), 87% with acalabrutinib monotherapy (P<.0001 vs obinutuzumab plus chlorambucil), and 47% with chlorambucil plus obinutuzumab. A post-hoc exploratory analysis favored the addition of obinutuzumab to acalabrutinib over acalabrutinib alone, with a hazard ratio of 0.49. No differences in overall survival were seen among the 3 treatment arms.

Several investigators have demonstrated the synergistic efficacy of combining B-cell receptor antagonists, most notably ibrutinib, with venetoclax. Although the preliminary data for this combination are excellent, 20% of patients required dose reductions and 7% discontinued the treatment owing to adverse events.[10] In order to take advantage of the synergy of these agents and improve tolerability, Dr Paul M. Barr and colleagues undertook a phase 1/2 trial of the combination of ublituximab, umbralisib, and venetoclax in relapsed and refractory CLL.[12] It is hoped that umbralisib, a phosphoinositide 3 (PI3) kinase delta inhibitor, will avoid many of the adverse events associated with ibrutinib. Treatment with umbralisib in combination with ublituximab and venetoclax was well tolerated, with only 2 of 27 patients discontinuing therapy. Using umbralisib plus ublituximab (known as U2) as a lead-in therapy, the number of patients at high or medium risk for tumor lysis syndrome was reduced from 65% to 13%. The regimen proved to be highly efficacious, with an ORR of 100% and a bone marrow MRD-negativity rate of 78% after 12 cycles of treatment. This novel regimen affords an opportunity to replicate the excellent efficacy data reported with ibrutinib plus venetoclax,[9,10] but with a different toxicity profile that might enable the treatment of additional patients.

Mantle Cell Lymphoma

Mantle cell lymphoma is currently incurable, and more treatment options are needed. CAR T cells have shown efficacy among patients with relapsed/refractory DLBCL.[13] The phase 2 ZUMA-2 trial investigated KTE-X19 CAR T-cell therapy in patients with relapsed and refractory mantle cell lymphoma.[14] KTE-X19 differs from axicabtagene ciloleucel (KTE-C19) in its manufacturing process that depletes circulating tumor cells. In 68 patients who received KTE-X19, the ORR was 93%, with a complete response rate of 67% and a partial response rate of 27%. After a median follow-up of 12.3 months, 57% of patients continued to respond, including 78% of those who achieved a complete response. Among the first 28 patients treated, 43% remained in remission at a median follow-up of 27 months. These data suggest that KTE-X19 is able to achieve responses in almost all relapsed/refractory mantle cell patients and may provide sustainable responses for some patients.

Diffuse Large B-Cell Lymphoma

Limiting exposure to unnecessary treatment is an important goal in B-cell malignancies. Dr Laurie H. Sehn presented data from a long-term follow-up analysis of a positron emission tomography (PET)-guided approach to the treatment of limited-stage DLBCL.[15] In the study, 319 patients underwent a PET/computed tomography scan after 3 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); 80% were PET-negative and 18% were PET-positive. Of the 254 PET-negative patients, 92% received 1 additional cycle of R-CHOP, 5% received radiotherapy, and 3% stopped treatment. Of the 59 PET-positive patients, 55 received radiotherapy, 2 received 3 additional cycles of R-CHOP, and 2 patients received 1 additional cycle of R-CHOP. After a median follow-up of 6.25 years, 21 of 254 PET-negative patients (8%) relapsed, compared with 13 of 59 PET-positive patients (22%). These data demonstrate that with a PET-guided approach to treatment, almost 80% of patients will

achieve a negative PET scan, and these patients can have excellent outcomes with only 1 more cycle of R-CHOP, thereby safely avoiding radiotherapy and its long-term toxicities.

Waldenström Macroglobulinemia

Dr Marie José Kersten presented results from a HOVON/ECWM phase 1/2 trial investigating the safety and efficacy of ixazomib plus rituximab and dexamethasone in the treatment of patients with Waldenström macroglobulinemia.[16] The trial demonstrated the safety of ixazomib at 4 mg orally given on days 1, 8, and 15, and moved this regimen forward as the phase 2 dose. With 45 of 59 patients completing 8 cycles, a 71% ORR was achieved, with 51% of patients achieving a partial response or better. Progression-free survival at 24 months was 56%. Treatment was well tolerated, particularly in comparison with the toxicities seen with proteasome inhibitors in this setting. These data confirm the efficacy previously seen with this regimen in Waldenström macroglobulinemia.[17]

A Proof-of-Concept Trial

Although ibrutinib demonstrates excellent response rates in patient with CLL, Waldenström macroglobulinemia, mantle cell lymphoma, and marginal zone lymphoma, a significant number of patients will demonstrate progressive disease.[18] One mechanism of resistance is the development of a single base pair mutation in the Bruton tyrosine kinase (*BTK*) gene leading to a replacement of the cysteine at position 481 with a serine. The loss of the sulfhydryl group on the cysteine removes the site where ibrutinib covalently binds to BTK and irreversibly blocks the ATP pocket.[19,20] Reversible inhibitors of BTK, such as vecabrutinib, ARQ-531, and LOXO-305, have the potential to overcome this resistance mutation because they do not need to covalently bind the sulfhydryl group to block the ATP pocket.[21] Dr Anthony R. Mato presented results of the first in-human, proof-of-concept phase 1 trial of LOXO-305.[22] The study examined LOXO-305 in a traditional phase 1 design, testing dose levels from 25 mg/day to 200 mg/day in patients with CLL and B-cell non-Hodgkin lymphoma who progressed during or were intolerant to BTK inhibitor therapy. Treatment was well tolerated, with no dose-limiting toxicities observed. The most common AEs were fatigue in 25% and diarrhea in 18%. Doses of 100 mg/day and higher achieved greater than 90% BTK inhibition over 24 hours. Responses were seen at all dose levels. The ORR was 77% in CLL and 50% in mantle cell lymphoma.

Disclosure

Dr Furman has received research funding from AstraZeneca and Janssen. He is a consultant for AbbVie, AstraZeneca, BeiGene, Genentech, Janssen, Loxo Oncology, OncoTracker, Pharmacyclics, TG Therapeutics, and Verastem Oncology. He has received speaker fees from AbbVie and Janssen, and is a member of the Data and Safety Monitoring Board for Incyte. He has provided expert testimony for AbbVie.

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