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A SPECIAL MEETING REVIEW EDITION

Highlights From the XVIII International Workshop on Chronic Lymphocytic Leukemia

A Review of Selected Presentations From the XVIII iwCLL • September 20-23, 2019 • Edinburgh, Scotland

Special Reporting on:

- Ibrutinib Versus Placebo in Patients With Asymptomatic, Treatment-Naive Early-Stage Chronic Lymphocytic Leukemia: Primary Endpoint Results of the Phase 3 Double-Blind Randomized CLL12 Trial
- Obinutuzumab and Ibrutinib Treatment Induction Followed by a Minimal Residual Disease–Driven Strategy in Chronic Lymphocytic Leukemia: Long-Term Results in the ICLL-07 FILO Trial
- Ibrutinib for First-Line Treatment of Chronic Lymphocytic Leukemia in Patients Aged ≥65 Years: Results With 5 Years of Follow-Up for the RESONATE-2 Study
- Obinutuzumab as Consolidation After Chemo-Immunotherapy Is Highly Effective in Achieving MRD Clearance From Bone Marrow and Peripheral Blood Resulting in Improved Progression-Free Survival: Results of UK NCRI Phase II/III GALACTIC Trial
- Final 5-Year Updated Results From a Phase 3 Study (HELIOS) of Ibrutinib Plus Bendamustine and Rituximab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Venetoclax Combined With Ibrutinib Based on a Minimal Residual Disease–Guided Approach in Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of the IMPROVE Study
- Ibrutinib Plus Venetoclax in Relapsed/Refractory CLL: The CLARITY Study
- ASCEND Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab Plus Idelalisib or Bendamustine in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia
- Treatment of CLL From 2019 Onwards

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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A National Comprehensive Cancer Network® (NCCN®) Recommendation

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

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

Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

INDICATIONS

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥Grade 3, serious, or 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.

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

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

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

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

Suggested treatment regimens for first-line therapy in CLL/SLL without del 17p/*TP53* mutation		
	Preferred regimens	**Other recommended regimens†** **(alphabetical by category)**
Frail patients with significant comorbidity **OR** **age ≥65 years and younger patients with significant comorbidities**	**Ibrutinib (IMBRUVICA®) (category 1)** Venetoclax + obinutuzumab (category 2A)	• Bendamustine + an anti-CD20 monoclonal antibody‡ (category 2A) • Chlorambucil + an anti-CD20 monoclonal antibody (category 2A) • High-dose methylprednisolone (HDMP) + rituximab (category 2B) • Ibrutinib + obinutuzumab (category 2B) • Obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients age <65 years without significant comorbidities	**Ibrutinib (IMBRUVICA®) (category 1)**	• Bendamustine + an anti-CD20 monoclonal antibody (category 2A) • FCR (fludarabine + cyclophosphamide + rituximab)§ (category 2A) • FR (fludarabine + rituximab)‖ (category 2A) • HDMP + rituximab (category 2B) • Venetoclax + obinutuzumab (category 2B) • Pentostatin, cyclophosphamide, rituximab (category 3)
Suggested treatment for first-line therapy in CLL/SLL with del 17p/*TP53* mutation		
All patients	**Ibrutinib (IMBRUVICA®) (category 2A)** Venetoclax + obinutuzumab (category 2A)	• Alemtuzumab +/- rituximab (category 2A) • HDMP + rituximab (category 2A) • Obinutuzumab (category 2A)

†See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for complete list of regimens.
‡Bendamustine + anti-CD20 MAB is not recommended for frail patients.
§FCR is appropriate first-line treatment for young, fit patients with mutated IGHV.
‖FR is not recommended for CLL with del(11q).

Categories of Evidence/Consensus
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Categories of Preference¶
Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).
¶All recommendations in the NCCN Guidelines are considered appropriate.

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

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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%).

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

Monitor patients closely and treat as appropriate.

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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imbruvica® (ibrutinib)

560, 420, 280, 140 mg tablets | 140, 70 mg capsules

 07/19 PRC-05663a

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. 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.

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 1 and 2.

Table 1: 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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
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 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

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

* Based on laboratory measurements per IWCLL criteria and adverse reactions.
Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

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

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

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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†
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

IMBRUVICA® (ibrutinib)

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

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

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

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

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

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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
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

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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 6 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

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

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
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
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.

IMBRUVICA® (ibrutinib)

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

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

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

Body System Adverse Reaction§	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
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.

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]*.

IMBRUVICA® (ibrutinib)

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 20 times the exposure in patients with CLL/SLL administered the dose of 420 mg daily. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights.

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

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

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

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

Contraception: Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions]*.
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions]*.
- *Cardiac Arrhythmias:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions]*.
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions]*.
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions]*.
- *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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PRC-05667

Ibrutinib Versus Placebo in Patients With Asymptomatic, Treatment-Naive Early-Stage Chronic Lymphocytic Leukemia: Primary Endpoint Results of the Phase 3 Double-Blind Randomized CLL12 Trial

A 1998 study of chlorambucil in patients with Binet stage A chronic lymphocytic leukemia (CLL) suggested that treatment of indolent disease was not beneficial.[1] Since that time, novel drugs with improved efficacy and less toxicity have been incorporated into the management of several subgroups of patients with CLL. The double-blind, randomized phase 3 CLL12 trial (Ibrutinib in Previously Untreated Binet Stage A Chronic Lymphocytic Leukemia With Risk of Disease Progression) evaluated the efficacy and safety of the Bruton tyrosine kinase (BTK) inhibitor ibrutinib as first-line treatment of patients with asymptomatic, Binet stage A CLL.[2] Among the 515 patients enrolled in the trial, 152 had low-risk disease and were assigned to the watch-and-wait arm. The remaining 363 patients were randomly assigned to receive ibrutinib (420 mg daily) or placebo. Risk of progression was intermediate in 273 patients, high in 82 patients, and very high in 8 patients. The primary endpoint was event-free survival from the time of randomization until symptomatic disease progression, initiation of new treatment, or death. Secondary endpoints evaluated survival, response, and safety.

The baseline characteristics were well balanced between the 2 arms. Among the 363 patients, the median age was 64 years (range, 36-85 years). Approximately 29% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. The median score on the Cumulative Illness Rating Scale (CIRS) was 2 (range, 0-14). The 17p deletion was reported in 3.3% of the ibrutinib arm and 3.9% of the placebo arm. The 11q deletion was observed in 11.5% vs 10.5%, respectively. The immunoglobulin heavy chain variable region gene (*IGHV*) was unmutated in 38.7% of the patients in each group. *TP53* was mutated in 7.7% of the ibrutinib arm and 7.2% of the placebo arm. The level of β2 microglobulin exceeded 3.5 mg/dL in 7.7% of patients in each arm, and more than three-fourths of patients in each arm had a thymidine kinase level higher than 10 U/L.

The median observation time was 31.0 months for both arms. The median treatment duration was 21 months (range, 1-57 months) in the ibrutinib arm vs 18 months (range, 1-57 months) in the placebo arm. Ten patients in each arm had not yet started study treatment. An additional 17 patients in the ibrutinib arm and 13 in the placebo arm had received no treatment at all. The study treatment was discontinued by 65 patients (34.1%) in the ibrutinib arm and 83 (45.9%) in the placebo arm. In the ibrutinib arm, the primary reason for treatment discontinuation was adverse events (AEs; 53 patients vs 26 patients). Most patients in the placebo arm discontinued treated owing to progressive disease (45 patients vs 2 patients). In the ibrutinib arm, 54.9% of patients remained on study treatment, vs 47% in the placebo arm.

Primary endpoint analysis showed a median event-free survival of not reached in the ibrutinib arm vs 47.8 months in the placebo arm (hazard ratio [HR], 0.248; *P*<.0001; Figure 1). The median progression-free survival (PFS) was not reached in the ibrutinib arm vs 14.8 months in the placebo arm

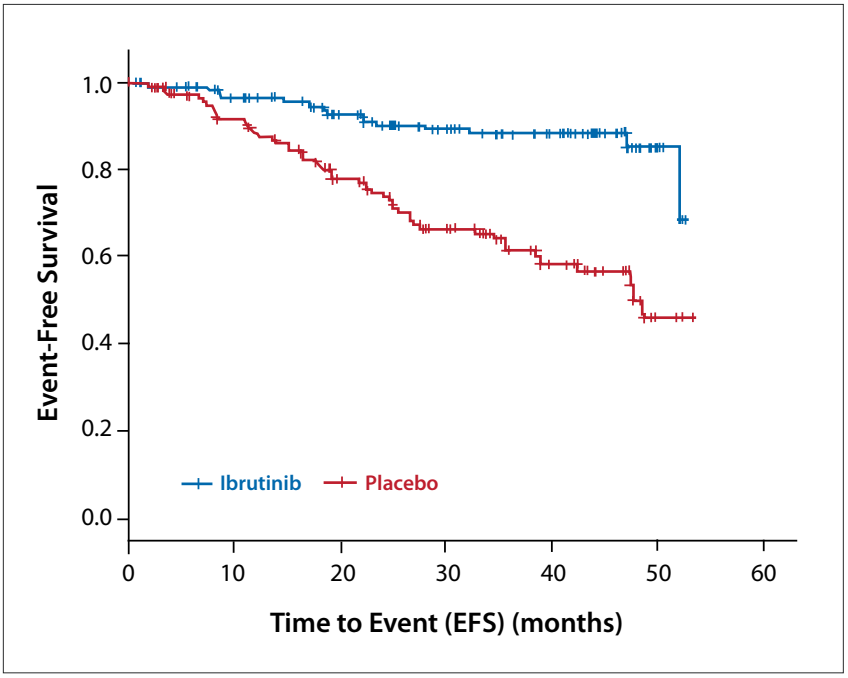

Figure 1. Event-free survival in the phase 3 CLL12 trial of patients with asymptomatic, treatment-naive, early-stage chronic lymphocytic leukemia. CLL12, Ibrutinib in Previously Untreated Binet Stage A Chronic Lymphocytic Leukemia With Risk of Disease Progression. EFS, event-free survival. Adapted from Langerbeins P et al. Abstract 1938. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[2]

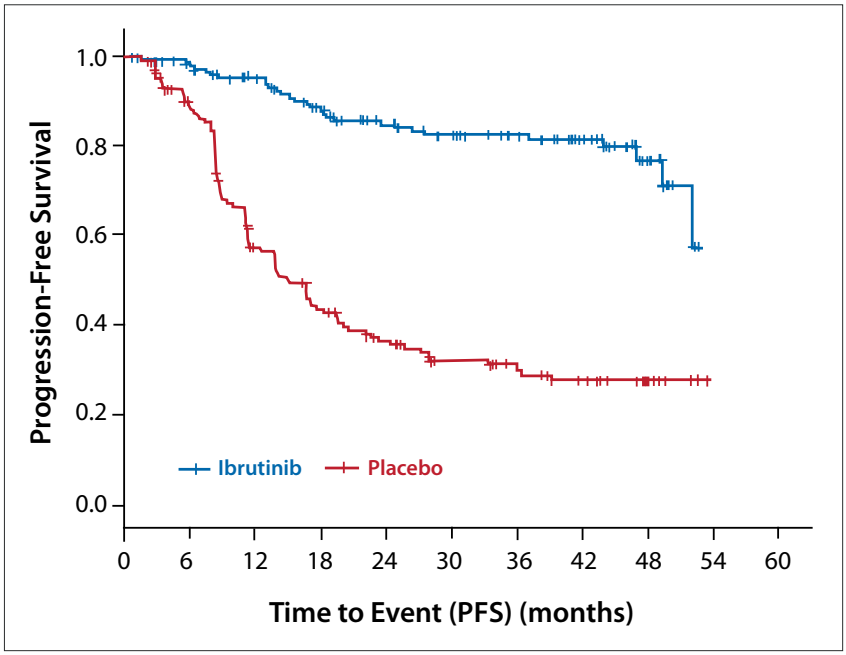

Figure 2. Progression-free survival in the phase 3 CLL12 trial of patients with asymptomatic, treatment-naive, early-stage chronic lymphocytic leukemia. CLL12, Ibrutinib in Previously Untreated Binet Stage A Chronic Lymphocytic Leukemia With Risk of Disease Progression. PFS, progression-free survival. Adapted from Langerbeins P et al. Abstract 1938. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[2]

(HR, 0.176; *P*<.0001; Figure 2). The median time to next treatment was also significantly prolonged in the ibrutinib arm (HR, 0.205; *P*<.0001).

Approximately 95% of patients in each arm developed an AE of any grade. AEs of grade 3 or higher were observed in 50.6% of patients in the ibrutinib arm and 43.2% of patients in the placebo arm. AEs required interruption of ibrutinib in 41.6% of patients and interruption of placebo in 21.3% of patients. The AEs that led to treatment interruption included arrhythmias (in 18 patients treated with ibrutinib vs 0 with placebo), bleeding (8 vs 1), diarrhea (4 vs 3), neoplasia (4 vs 3), infection (3 vs 4), and myocardial infarction (1 vs 3). In the ibrutinib vs the placebo arm, the most common serious AEs included infections (12% each), neoplasms (7% vs 12%), and cardiac disorders (10% vs 6%). Any-grade AEs of special clinical interest that occurred at a higher rate in the ibrutinib arm included bleeding (32.3% vs 10.3%; *P*=.000), atrial fibrillation (20.9% vs 7.7%; *P*=.001), and hypertensive disorders (11.4% vs 4.5%; *P*=.04). Fatal AEs occurred in 2.5% of the ibrutinib arm vs 3.2% of the placebo arm, but none of the events were related to treatment.

Until data from the full survival analysis are available, the study authors recommend a watch-and-wait strategy for early-stage patients who have an increased risk of progression.

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Obinutuzumab and Ibrutinib Treatment Induction Followed by a Minimal Residual Disease–Driven Strategy in Chronic Lymphocytic Leukemia: Long-Term Results in the ICLL-07 FILO Trial

For many years, chemoimmunotherapy consisting of fludarabine, cyclophosphamide, and rituximab (FCR) has been the treatment of choice for medically fit patients with CLL who have wild-type *TP53*.[1] In the CLL8 trial (Fludarabine and Cyclophosphamide With or Without Rituximab in Patients With Previously Untreated Chronic B-Cell Lymphocytic Leukemia), reported in 2012, longer PFS and overall survival (OS) were seen among patients with a clinical complete response (CR) plus a level of minimal residual disease (MRD) below 0.01% (as measured in the bone marrow).[2] The phase 2 ICLL-07 trial (Obinutuzumab and Ibrutinib Induction Therapy Followed by a Minimal Residual Disease-Driven Strategy in Patients With Chronic Lymphocytic Leukaemia) evaluated a treatment strategy in which the second course of therapy was determined by the patient's response and MRD status following initial therapy.[3] This multicenter, open-label trial enrolled treatment-naive, medically fit patients without the 17p deletion. Patients had a CIRS score of 6 or lower.

During part 1 of the study, patients received 8 doses of obinutuzumab (1000 mg) over 6 cycles of 4 weeks

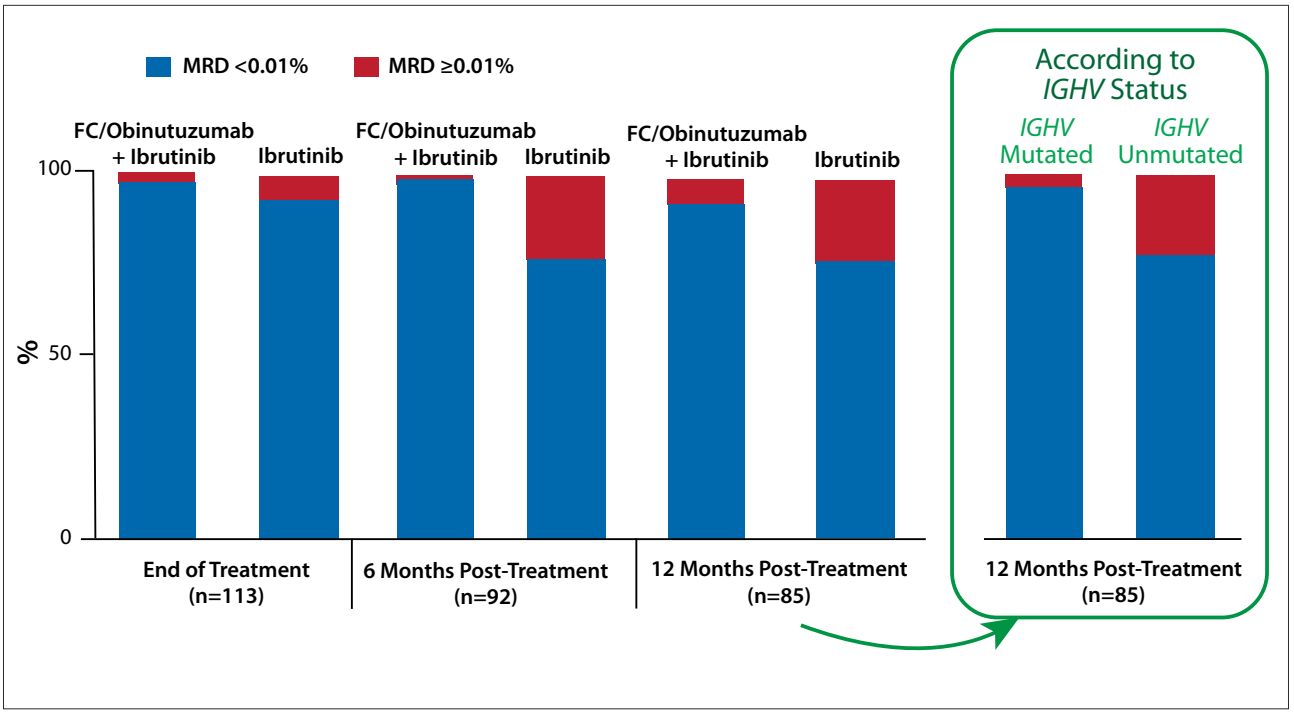

Figure 3. The phase 2 ICLL-07 trial assessed levels of MRD to guide treatment. Results of longitudinal follow-up are shown. FC, fludarabine and cyclophosphamide; *IGHV*, immunoglobulin heavy chain variable region gene; MRD, minimal residual disease. Adapted from Michallet AS et al. Abstract 1962. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[3]

each, plus daily ibrutinib (420 mg) for 9 months. During part 2 of the study, patients received different treatments based on an assessment performed on day 1 of month 9. Patients with a CR and a bone marrow MRD of less than 0.01% continued treatment with ibrutinib monotherapy (420 mg daily) for 6 additional months. All other patients received 4 cycles of FC plus obinutuzumab (1000 mg), administered every 4 weeks for 4 cycles, plus daily ibrutinib (420 mg) for 6 months. The assessment of CR was based on criteria from the International Workshop on CLL (iwCLL).[4] The primary objective was to demonstrate an increase of at least 30% in the rate of CR plus MRD below 0.01% by month 16, based on an intention-to-treat analysis.

The trial enrolled 135 patients, and 130 were randomly assigned to treatment. The patients' median age was 65 years (range, 35-80 years), and two-thirds were male. Seven percent of patients had active stage A disease, 67% had active stage B disease, and 26% had stage C disease. Fifty-six percent had unmutated *IGHV*, 26% had the 11q deletion, and 15% had a complex karyotype. The median rate of creatinine clearance was 82 mL/min (range, 42-173.5 mL/min). Based on the evaluation on day 1 of month 9, 10 patients had a CR plus an MRD level of less than 0.01%. These patients continued treatment with daily ibrutinib monotherapy in part 2 of the study. The remaining 120 had a partial response (PR) or a CR, plus a bone marrow MRD level of 0.01%

ABSTRACT SUMMARY Time-Limited Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia: First Presentation of 4-Year Data From the MURANO Study

In the phase 3 MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL]), patients with CLL were randomly assigned to receive either 6 cycles of venetoclax plus rituximab followed by daily venetoclax for 2 years or 6 cycles of bendamustine/rituximab (Abstract 2266). At a median follow-up of 48 months, fixed-duration treatment with venetoclax/rituximab continued to yield a superior median PFS (HR, 0.19; 95% CI, 0.14-0.25; *P*<.0001) and OS (HR, 0.41; 95% CI, 0.26-0.65; *P*<.0001) vs bendamustine/rituximab, despite the fact that 79% of patients in the bendamustine/rituximab arm received a novel therapy for their CLL after disease progression. Estimated 4-year PFS was 57.3% with venetoclax/rituximab vs 4.6% with bendamustine/rituximab. Rates of estimated 4-year OS were 85.3% vs 66.8%, respectively.

ABSTRACT SUMMARY Patient-Reported Outcomes Monitoring Dramatically Improves Therapy Adherence and Overall Survival in Ibrutinib-Exposed Patients: A Retrospective Study From the FILO Group

A retrospective study evaluated the impact of a patient monitoring program on outcomes in patients with CLL who received ibrutinib as first-line therapy or in later settings (Abstract 1989). The Ambulatory Patients Monitoring and Assistance (AMA) program was developed to preemptively manage side effects and to provide ongoing education to promote adherence to therapy. The study enrolled more than 450 patients, and 30% received AMA support. The program was implemented during the first 12 months of ibrutinib therapy. After a median follow-up of 27.4 months, median OS was superior in the AMA group vs the control group ($P<.0001$). Symptom monitoring by an AMA oncology nurse reduced the risk of premature discontinuation of ibrutinib during the first year (19.3% vs 44.2%) by reducing toxicities that could lead to discontinuation (18.6% vs 30.3%). Multivariate analysis showed that AMA monitoring was an independent prognostic factor associated with OS ($P<.0001$).

or higher. Among these patients, 115 received daily ibrutinib as well as FC plus obinutuzumab in part 2.

In the intention-to-treat analysis, at month 16, 73% of patients had a CR and 79% had a bone marrow MRD level of less than 0.01%. Both of these outcomes combined were seen in 62% of patients. An MRD level of less than 0.01% was more common among patients with the *IGHV* mutation vs without the mutation (Figure 3). After a median follow-up of 26.3 months, 2-year PFS was 97.0% and 2-year OS was 97.5%.

In part 1 of the study, the most common grade 3/4 hematologic AEs included thrombocytopenia (31%), neutropenia (24%), and anemia (5%). The most common nonhematologic AEs were infusion-related reactions (8%), gastrointestinal disorders (3%), and cardiac events (2.2%). In part 2, the most common grade 3/4 AEs among all patients included neutropenia (24%), thrombocytopenia (15%), and gastrointestinal disorders (10%).

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Ibrutinib for First-Line Treatment of Chronic Lymphocytic Leukemia in Patients Aged ≥65 Years: Results With 5 Years of Follow-Up for the RESONATE-2 Study

The international, open-label phase 3 RESONATE-2 trial (Open-Label Phase 3 BTK Inhibitor Ibrutinib vs Chlorambucil Patients 65 Years or Older With Treatment-Naive CLL or SLL) randomly assigned older patients with CLL to receive first-line treatment with ibrutinib or chlorambucil.[1] The trial enrolled patients ages 70 years or older, or patients ages 65 years to 69 years with comorbidities. Patients had CLL or small lymphocytic lymphoma (SLL) requiring therapy. Patients with the 17p deletion were excluded from the trial. Patients were stratified by ECOG performance status and Rai disease stage before treatment. The trial randomly assigned 136 patients to ibrutinib (420 mg daily) and 133 patients to 12 cycles of chlorambucil (0.5 mg/kg to a maximum of 0.8 mg/kg, administered on days 1 and 15 in 28-day cycles). The primary endpoint was PFS assessed by independent review. Secondary endpoints included OS, the objective response rate (ORR), sustained hematologic improvement, and safety.

The baseline characteristics were generally well balanced between the 2 arms. The 269 patients were a median age of 73 years (range, 65-90 years). Approximately 63% of patients were male, and 43% had an ECOG performance status of 0. Forty-five percent of patients had Rai stage III/IV disease, 32% had a CIRS score higher than 6, and 35% had bulky disease. Twenty-two percent of patients had the 11q deletion, and 58% had unmutated *IGHV*. The *TP53* mutation was reported in 10% of patients (12/124) in the ibrutinib arm vs 3% (3/94) in the chlorambucil arm. A high prognostic risk was reported in

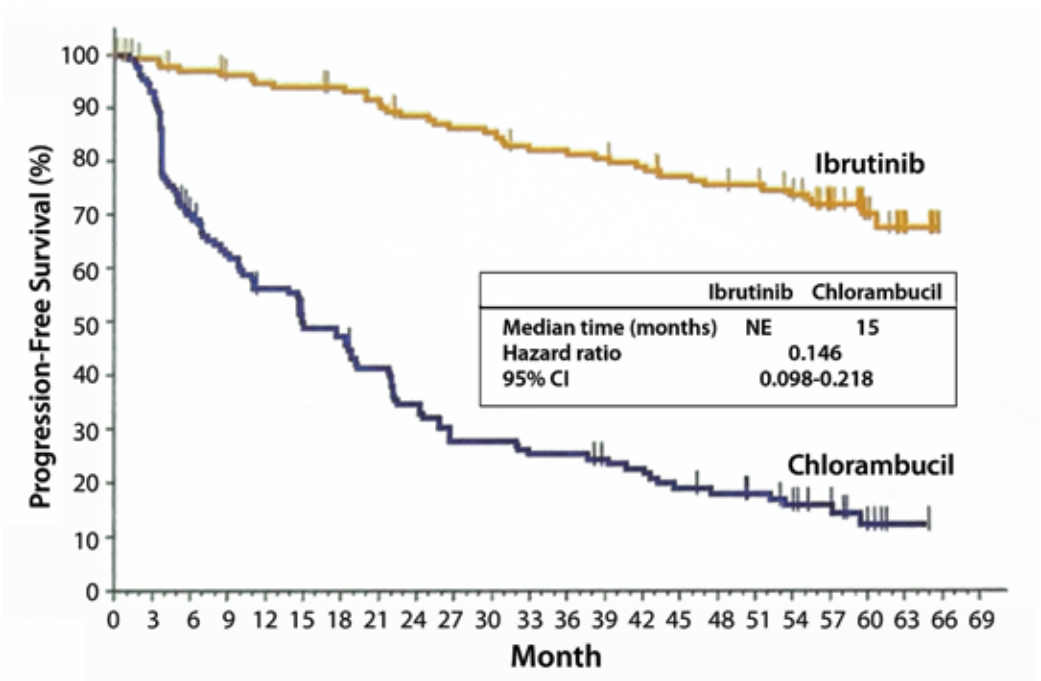

Figure 4. Progression-free survival in a 5-year analysis of the phase 3 RESONATE-2 trial. NE, not evaluable; RESONATE-2, Open-Label Phase 3 BTK Inhibitor Ibrutinib vs Chlorambucil Patients 65 Years or Older With Treatment-Naive CLL or SLL. Adapted from Tedeschi A et al. Abstract 1956. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[2]

53% of patients overall. After a median follow-up of 18.4 months, the median PFS was not reached with ibrutinib vs 18.9 months with chlorambucil (HR, 0.16; *P*<.001). The 2-year OS was 98% with ibrutinib vs 85% with placebo (HR, 0.16; *P*=.001).

After a median follow-up of 5 years (range, 0.1-66 months), 79 patients (58%) in the ibrutinib arm continued to receive the BTK inhibitor as part of the study.[2] The median duration of ibrutinib treatment was 57.1 months (range, 0.7-66.0 months), and 27% of patients had received ibrutinib for longer than 5 years. Twenty-nine patients discontinued ibrutinib owing to an AE.

Long-term follow-up underscored the benefits of ibrutinib compared with chlorambucil. The median PFS was not evaluable with ibrutinib vs 15.0 months with chlorambucil (HR, 0.146; 95% CI, 0.098-0.218; Figure 4). The estimated 5-year OS was 83% with ibrutinib vs 68% with chlorambucil (HR, 0.450; 95% CI, 0.266-0.761). Ibrutinib maintained a PFS improvement vs chlorambucil regardless of whether patients had the 11q deletion or *IGHV* mutations. The HRs for median PFS were 0.034 (95% CI, 0.010-0.108) in patients with the 11q deletion, 0.205 (95% CI, 0.132-0.318) in patients without

ABSTRACT SUMMARY Ibrutinib Improves Survival for Relapsed or Refractory Chronic Lymphocytic Leukemia After First-Line Chemoimmunotherapy: Population-Based Outcomes From 677 Patients Treated in British Columbia

A retrospective analysis evaluated outcomes among 677 patients with CLL/SLL in a single Canadian province who were treated with first-line fludarabine and rituximab and then received ibrutinib or another standard treatment as second-line therapy (Abstract 2041). Treatment with fludarabine and rituximab was associated with a 2-year OS of 89% and a 5-year OS of 73%. Median OS was 11.7 years, and median treatment-free survival was 3.8 years. Among 351 patients who received second-line therapy after fludarabine and rituximab, 25% received ibrutinib. After a median follow-up of 2.8 years, median OS was not reached with ibrutinib vs 5.3 years with any other second-line therapy (*P*<.001). Second-line ibrutinib also yielded a superior median treatment-free survival (not reached vs 1.2 years; *P*<.001).

the 11q deletion, 0.105 in those with unmutated *IGHV* (95% CI, 0.058-0.190), and 0.153 (95% CI, 0.067-0.349) in those with mutated *IGHV*. Among patients treated with ibrutinib, the ORR was 92%. The rate of CR/incomplete CR increased from 11% after 18 months of follow-up to 30% with long-term follow-up.[1,2]

In the ibrutinib arm, AEs of any grade and grade 3/4 occurred most frequently during the first year of treatment. The most common grade 3/4 AEs in the ibrutinib arm were neutropenia (13%), pneumonia (12%), hypertension (8%), anemia (7%), hyponatremia (6%), atrial fibrillation (5%), and cataracts (5%). Among the 27 patients who developed AEs that led to a dose reduction of ibrutinib, these events improved or resolved in 25 (93%). During the 5 years of the study, an AE was the primary cause of treatment discontinuation in 29 patients. Ibrutinib administration was interrupted for 7 or more consecutive days in 70 patients.

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Obinutuzumab as Consolidation After Chemo-Immunotherapy Is Highly Effective in Achieving MRD Clearance From Bone Marrow and Peripheral Blood Resulting in Improved Progression-Free Survival: Results of UK NCRI Phase II/III GALACTIC Trial

MRD negativity is an independent predictor of survival among patients with CLL, regardless of treatment.[1] The GALACTIC trial (GA101 [Obinutuzumab] Monoclonal Antibody as Consolidation Therapy in CLL) was a seamless phase 2/3 study that evaluated the ability of obinutuzumab to eradicate MRD when administered as consolidation therapy after immunochemotherapy in patients with B-cell CLL.[2] The multicenter, parallel-group, open-label trial enrolled adults who had received between 1 and 3 prior lines of therapy and whose most recent outcome was a PR or better. Prior therapy had ended between 3 and 24 months before study enrollment. The study excluded patients with a lymph node larger than 1.5 cm. The primary endpoint of the trial was undetectable MRD (<0.01%) at 6 months after randomization.

The planned enrollment of 188 patients was not met. The trial was terminated in January 2017 after enrollment of 48 patients. The 29 patients with positive MRD (>0.01%) were randomly assigned to consolidation therapy with obinutuzumab (n=14) or no consolidation therapy (n=15). Among patients in the consolidation cohort, their most recent prior treatment led to a CR in 7 and a PR in 7. Fifty-five percent of the patients randomly assigned to obinutuzumab had an MRD level higher than 0.3% at study entry. Twelve of these patients (86%) received all planned obinutuzumab infusions, and 2 patients missed a planned dose after developing hematologic dose-limiting toxicity.

At 6 months after randomization, 10 of the 14 patients (71.4%) who received obinutuzumab consolidation achieved undetectable MRD in the bone marrow. MRD was also undetectable in all 13 blood samples that were available for analysis. The median OS was similar for the consolidation and control arms (*P*=.2491). The median PFS, however, was not reached

ABSTRACT SUMMARY: Long-Term Efficacy and Safety of Maintenance With Lenalidomide in Patients With Chronic Lymphocytic Leukemia and a High Risk of Progression After First-Line Immunochemotherapy

The CLLM1 study evaluated maintenance lenalidomide among patients with CLL with high-risk disease after first-line immunochemotherapy (Abstract 2017). Among patients who responded to FCR, FC, or bendamustine/rituximab, those with an MRD of 10^{-2} or higher and those with an MRD of 10^{-4} or higher plus high-risk genetics were randomly assigned to receive maintenance lenalidomide (n=60) or placebo (n=29). After a median follow-up of 48 months, lenalidomide treatment was associated with a superior median PFS vs placebo (HR, 0.226; 95% CI, 0.128-0.399; *P*<.001). Maintenance lenalidomide also prolonged the time to next treatment (HR, 0.351; 95% CI, 0.185-0.665; *P*=.001). Eight patients (13.3%) in the lenalidomide arm achieved undetectable MRD vs none in the placebo arm. Three patients (5.4%) in the lenalidomide arm developed B-cell acute lymphoblastic leukemia.

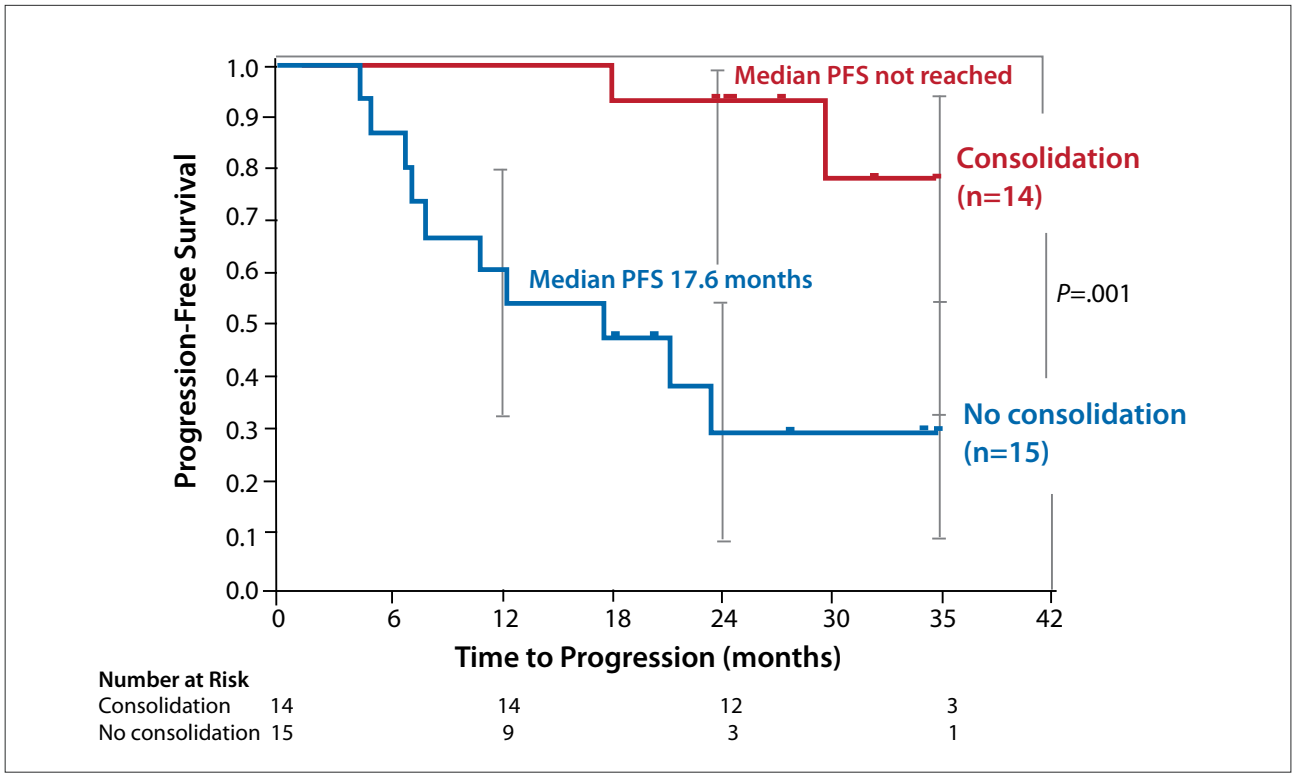

Figure 5. Progression-free survival in the phase 2/3 GALACTIC trial, which evaluated consolidation with obinutuzumab. GALACTIC, GA101 (Obinutuzumab) Monoclonal Antibody as Consolidation Therapy in CLL; PFS, progression-free survival. Adapted from Munir T et al. Abstract 2121. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[2]

in the obinutuzumab consolidation arm vs 17.6 months in the control arm (*P*=.001; Figure 5). Similar rates of PFS and OS were observed in patients who achieved MRD negativity after chemoimmunotherapy (n=19) or after consolidation with obinutuzumab (n=10). The most common AEs in the obinutuzumab consolidation arm included thrombocytopenia (22%), infection (9%), and cough (8%).

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Final 5-Year Updated Results From a Phase 3 Study (HELIOS) of Ibrutinib Plus Bendamustine and Rituximab in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The double-blind, phase 3 HELIOS study (A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma) compared the 3-drug combination of ibrutinib plus bendamustine/rituximab vs placebo plus bendamustine/rituximab in patients with relapsed or refractory CLL/SLL.[1,2] Conducted at 133 sites in 21 countries, the study enrolled 578 patients with previously treated CLL/SLL without the 17p deletion. Patients were randomly assigned to treatment in the ibrutinib or placebo arm. Patients first received up to 6 cycles of bendamustine and rituximab, plus either ibrutinib or placebo. Treatment then continued with either ibrutinib or

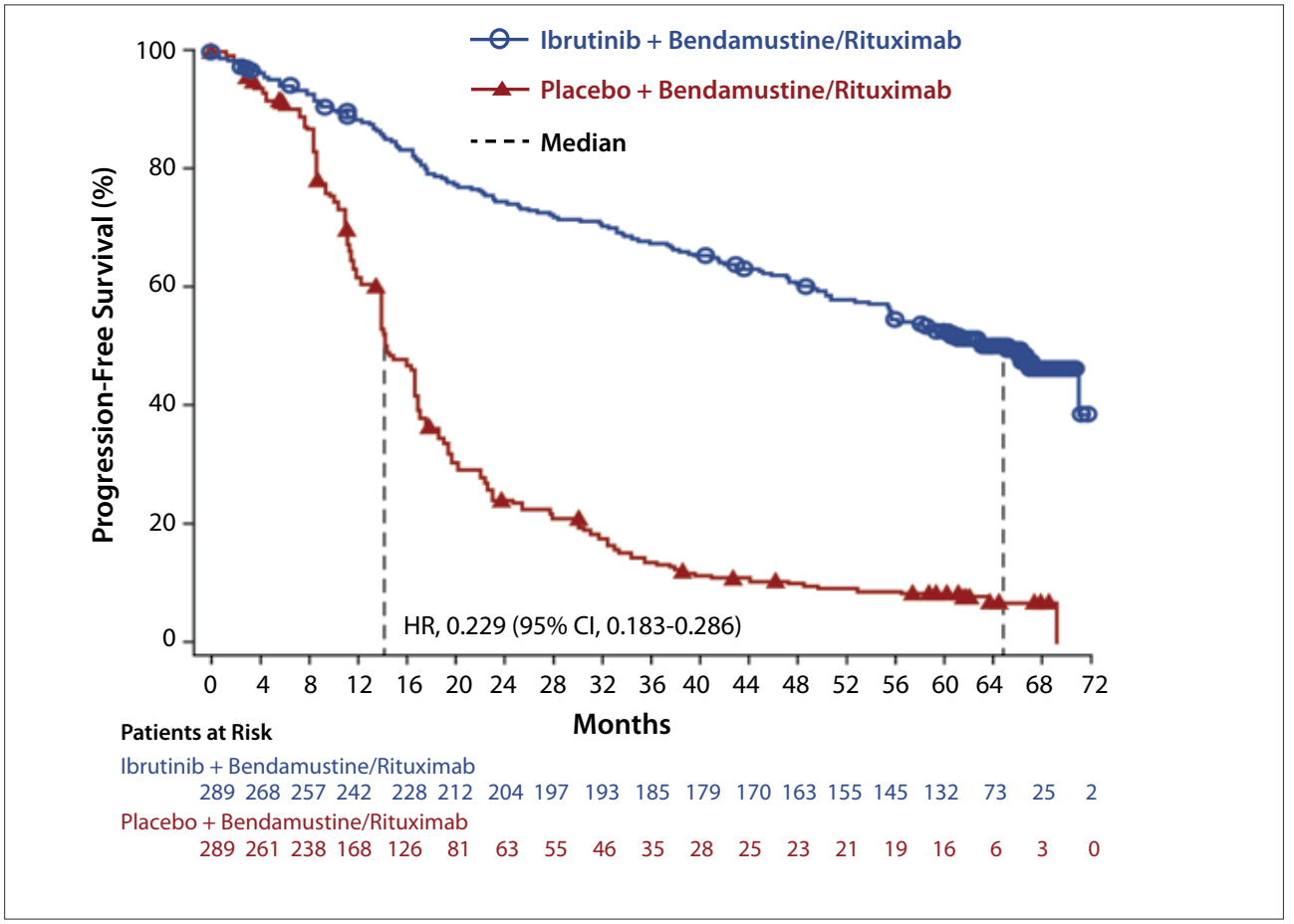

Figure 6. Progression-free survival in a 5-year analysis of the phase 3 HELIOS trial. HELIOS, Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; HR, hazard ratio. Adapted from Fraser G et al. Abstract 2021. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[3]

placebo alone until the patient developed progressive disease or unacceptable toxicity. Patients in the placebo arm who developed progressive disease were permitted to cross over to the ibrutinib group.

After an initial median follow-up of 17 months, the addition of ibrutinib to bendamustine/rituximab significantly improved median PFS (HR, 0.203; 95% CI, 0.150-0.276; *P*<.0001).[1] After a median follow-up of 34.8 months, ibrutinib plus bendamustine/rituximab continued to show a PFS benefit vs placebo plus bendamustine/rituximab (HR, 0.206; 95% CI, 0.159-0.265; *P*<.0001).[2]

The final analysis of the HELIOS study was conducted after a median follow-up of 63.7 months.[3] Patients received ibrutinib monotherapy for a median of 55.7 months (range, 0.2-72.9 months). In the ibrutinib arm, the most common reason for discontinuation of study treatment was a decision by the investigator or sponsor (reported in 47.1% of cases), which was most often made because the patient reached the end of the study period. Other common reasons that patients stopped ibrutinib included AEs (in 20.1%) and progressive disease or relapse (in 19.0%). In the placebo arm, the most common reason for discontinuation was progressive disease or relapse (in 51.2%). The next most common reason was investigator or sponsor decision (in 29.1%), mostly occurring after unblinding at the primary analysis.

Median PFS was 65.1 months among patients in the ibrutinib plus bendamustine/rituximab arm vs 14.3 months among those in the comparator arm (HR, 0.229; 95% CI, 0.183-0.286; *P*<.0001; Figure 6). Despite the fact that 183 patients in the placebo arm had crossed over to the ibrutinib arm, the 5-year analysis showed an OS advantage with the addition of ibrutinib to bendamustine/rituximab (HR, 0.611; 95% CI, 0.455-0.822; *P*=.0010). The median OS was not reached for either arm. The 5-year rate of OS was 75.7% with ibrutinib plus bendamustine/rituximab vs 61.2% with bendamustine/rituximab alone.

The ibrutinib regimen also yielded a superior ORR, at 87.2% vs 66.1%, respectively (P<.0001). The responses deepened over time.

The rates of treatment-emergent AEs in the ibrutinib arm were consistent with previous reports. Grade 5 treatment-emergent AEs of interest included infections and infestations (3.8%) and bleeding (1.0%).

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Venetoclax Combined With Ibrutinib Based on a Minimal Residual Disease–Guided Approach in Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of the IMPROVE Study

The combination of ibrutinib plus venetoclax is generally well tolerated among patients with relapsed or refractory CLL. This treatment elicits a high response rate, including high proportions of CRs and low or undetectable levels of MRD.[1,2] Venetoclax monotherapy can also result in undetectable MRD in some patients.[3]

The IMPROVE study was a single-arm, phase 2 trial that evaluated initial treatment with venetoclax, followed by the addition of ibrutinib based on MRD status, in patients with previously treated CLL.[4] The study enrolled patients with relapsed or refractory CLL who had no prior exposure to BTK or Bcl-2 inhibitors. Patients initially received venetoclax (starting at 20 mg daily, and increased to 400 mg daily) for up to 12 cycles. On day 1 of cycle 12, patients were evaluated for MRD in the peripheral blood and bone marrow. Patients with undetectable MRD (defined as $<10^{-4}$) in both the blood and bone marrow continued venetoclax monotherapy through the end of cycle 12 and then were monitored periodically for MRD. Patients with detectable MRD on day 1 of cycle 12 continued treatment with venetoclax, and also received ibrutinib (420 mg daily) starting on day 1 of cycle 13. Combination treatment was continued through a maximum of 24 cycles of 28 days each, at which point responding patients with detectable MRD continued on ibrutinib monotherapy. The primary endpoint was undetectable MRD ($<10^{-4}$) in both the peripheral blood and bone marrow.

Among the 38 patients, the median age was 64 years (range, 47-81 years). Sixty-one percent had bulky disease exceeding 5 cm, and 90% had Binet stage B/C disease. Most patients had genetic risk factors, and 55% were at high risk for tumor lysis syndrome. After 12 treatment cycles, the ORR was 92%, including a CR rate of 18% (Figure 7). MRD levels of less than

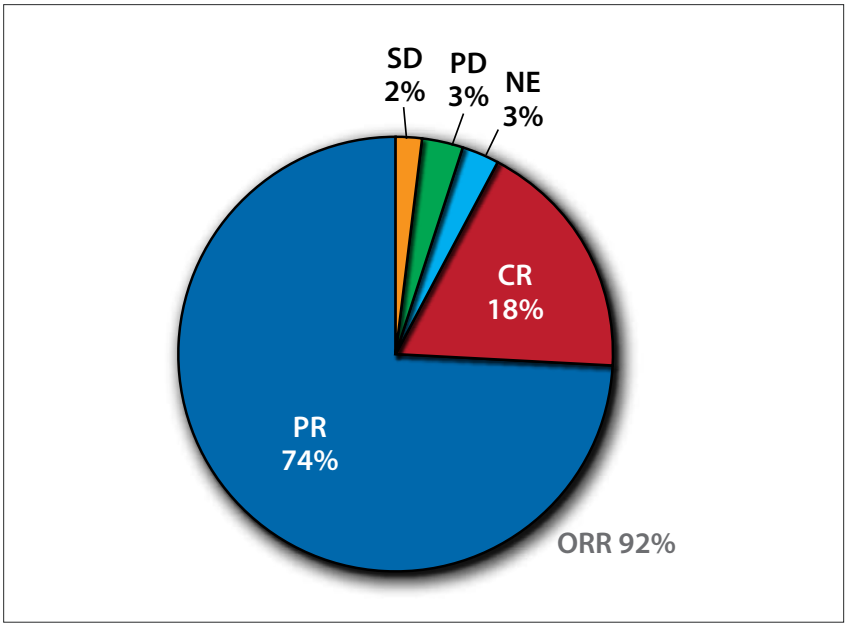

Figure 7. Response rates after 12 treatment cycles in the phase 2 IMPROVE study, which evaluated initial treatment with venetoclax, followed by the addition of ibrutinib based on MRD status, in patients with previously treated chronic lymphocytic leukemia. CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Scarfo L et al. Abstract 2068. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[4]

ABSTRACT SUMMARY: A Phase 2 Study to Assess the Safety and Efficacy of Umbralisib in Patients With Chronic Lymphocytic Leukemia Who Are Intolerant to Prior BTK or PI3K Delta Inhibitor Therapy

A phase 2 study evaluated umbralisib in 51 patients with CLL who were unable to tolerate prior therapy with a BTK or PI3Kδ inhibitor (Abstract 1943). After a median follow-up of 15.7 months, 58% of patients had received umbralisib for a longer duration compared with their prior kinase inhibitor. The trial met its primary endpoint, with a median PFS of 23.5 months (95% CI, 13.1 months to not evaluable). Umbralisib was generally well tolerated, with no fatal AEs. Six patients (12%) discontinued treatment after developing an AE that was related to umbralisib. One patient (2%) discontinued owing to an AE that also occurred with prior ibrutinib treatment.

10^{-4} were observed in 45% of patients. After a median follow-up of 14 months (range, 6-22 months), the proportion of patients with undetectable MRD had increased during 12 cycles of venetoclax monotherapy and with the MRD-based addition of ibrutinib.

No clinical or laboratory tumor lysis syndrome occurred. Two serious AEs were observed, both of which were considered unrelated to study treatment. Among the 12 cases of grade 3/4 AEs, the most common was neutropenia (9 events).

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Ibrutinib Plus Venetoclax in Relapsed/Refractory CLL: The CLARITY Study

The phase 2 CLARITY trial (Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia) investigated ibrutinib plus venetoclax in patients with relapsed or refractory CLL.[1,2] Enrolled patients required therapy based on iwCLL criteria. They had either relapsed within 3 years of prior immunochemotherapy or had the 17p deletion after at least 1 prior regimen. After 8 weeks of single-agent ibrutinib (420 mg daily), patients then received additional venetoclax, starting at a dose of 10 mg or 20 mg daily and escalating to a final dose of 400 mg daily. Peripheral blood and bone marrow samples were assessed at months 8, 14, and 26, with additional peripheral blood samples taken at various time points. The primary endpoint was undetectable MRD in the bone marrow, defined as less than 0.01% CLL cells and assessed by 6- or 8-color flow cytometry, after 12 months of combination treatment.

The presentation provided data for 50 patients. Their median age was 64 years (range, 31-83 years). Seventy-two percent had Binet stage B/C disease, and 8% had bulky lymph nodes. Seventy-four percent had unmutated *IGHV*, 20% had the 17p deletion, and 25% had the 11q deletion. The median number of prior therapies was 1 (range, 1-6).

After 12 months of ibrutinib plus venetoclax, 29 of 50 patients (58%) had undetectable MRD in the peripheral blood, and 20 of 50 (40%) had undetectable MRD in the bone marrow. Among patients who had relapsed within 3 years of prior FCR or bendamustine/rituximab, the rates of MRD negativity were 70% (14/20) in the peripheral blood and 45% (9/20) in the bone marrow. Peripheral blood and bone marrow analysis showed a continuous increase in MRD negativity from screening (n=50) through week 26 (n=46; Figure 8). Among 17 patients who achieved undetectable MRD at month 8 or month 14, 16 (94%) reached month 26 and remained MRD-negative. Among 46 patients who were evaluable at month 26, MRD negativity of less than 0.01% was reported in 32 (70%) with peripheral blood assays and in 23 (50%) with bone marrow assays. MRD negativity of less than 10^{-5} was detected in the peripheral blood of 21 patients (46%) and in the bone marrow of 13 patients (28%). Among all 50 patients, the ORR assessed at month 14 was 96%, including a rate of CR plus incomplete CR of 56%. One case of tumor lysis syndrome was successfully managed by delaying venetoclax escalation. One patient achieved an MRD-positive CR during the CLARITY study, but later developed disease progression with Richter transformation and died.

An in-depth analysis of paired peripheral blood and bone marrow samples demonstrated a high correlation in MRD levels. Based on 142 paired samples taken at month 8 or

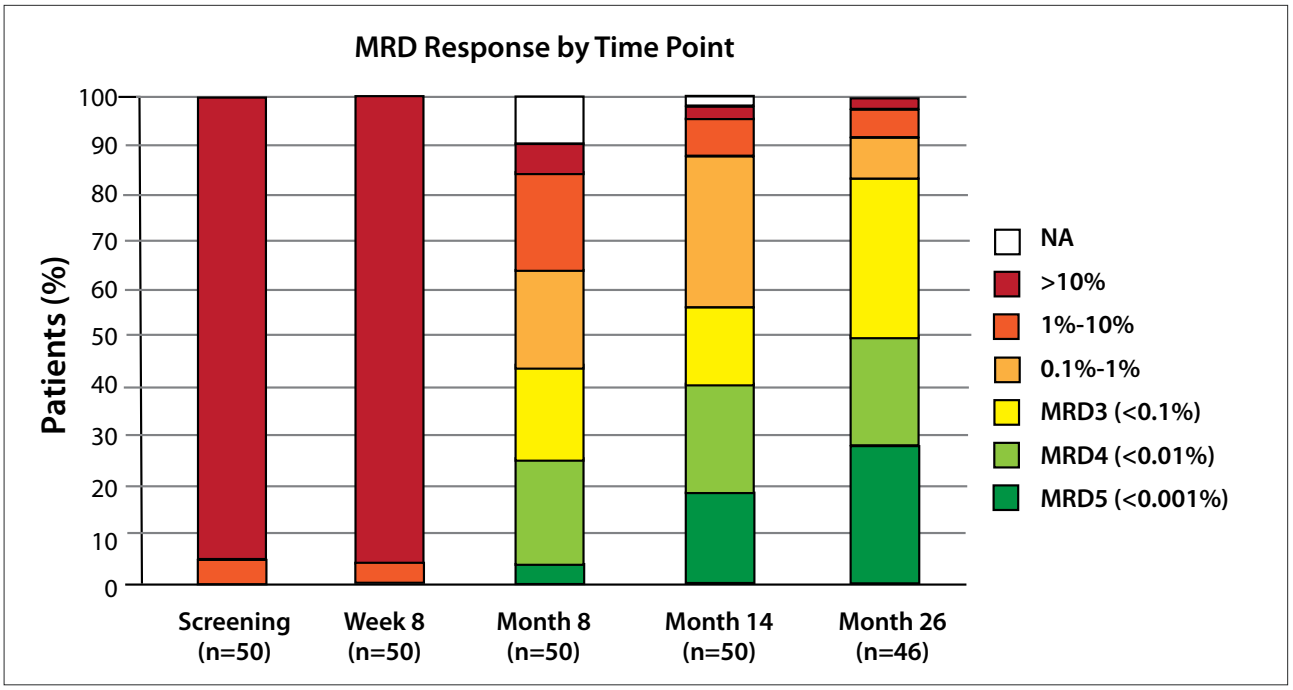

Figure 8. MRD response as measured in the bone marrow in the phase 2 CLARITY trial, which evaluated ibrutinib plus venetoclax in patients with relapsed or refractory chronic lymphocytic leukemia. CLARITY, Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia; MRD, minimal residual disease; NA, not available. Adapted from Munir T et al. Abstract 2143. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[1]

later, bone marrow levels of CLL cells were a median of 0.48 logs higher than in the peripheral blood. After 6 months of study treatment, 16 of 48 evaluable patients (34%) had achieved less than 0.01% CLL cells in the peripheral blood, and all of these patients achieved less than 10^{-4} bone marrow MRD after 12 months of study treatment. In contrast, among 26 patients whose peripheral blood showed greater than 0.01% CLL cells, only 3 patients (12%) subsequently achieved bone marrow MRD of less than 0.01% after 12 months of study treatment. Exposure to ibrutinib and venetoclax resulted in changes in the expression of Bcl-2 and Bax.

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ASCEND Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab Plus Idelalisib or Bendamustine in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

Rituximab given in combination with either bendamustine or idelalisib is a standard therapy for patients with relapsed or refractory CLL.[1] Acalabrutinib is a BTK inhibitor that has demonstrated less off-target kinase inhibition in vitro compared with ibrutinib.[2] The global, open-label, phase 3 ASCEND trial (A Study of Acalabrutinib vs Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in R/R CLL) evaluated acalabrutinib monotherapy vs idelalisib/rituximab or bendamustine/rituximab in patients with relapsed or refractory CLL.[3] Prior to random assignment to therapy, patients were stratified based on 17p deletion status, ECOG performance status, and number of prior therapies. Acalabrutinib was administered at a dose of 100 mg twice daily. In the combination arms, patients were treated with rituximab (initially administered at 375 mg/m^2, with subsequent doses of 500 mg/m^2) plus either idelalisib (150 mg, twice daily) or bendamustine

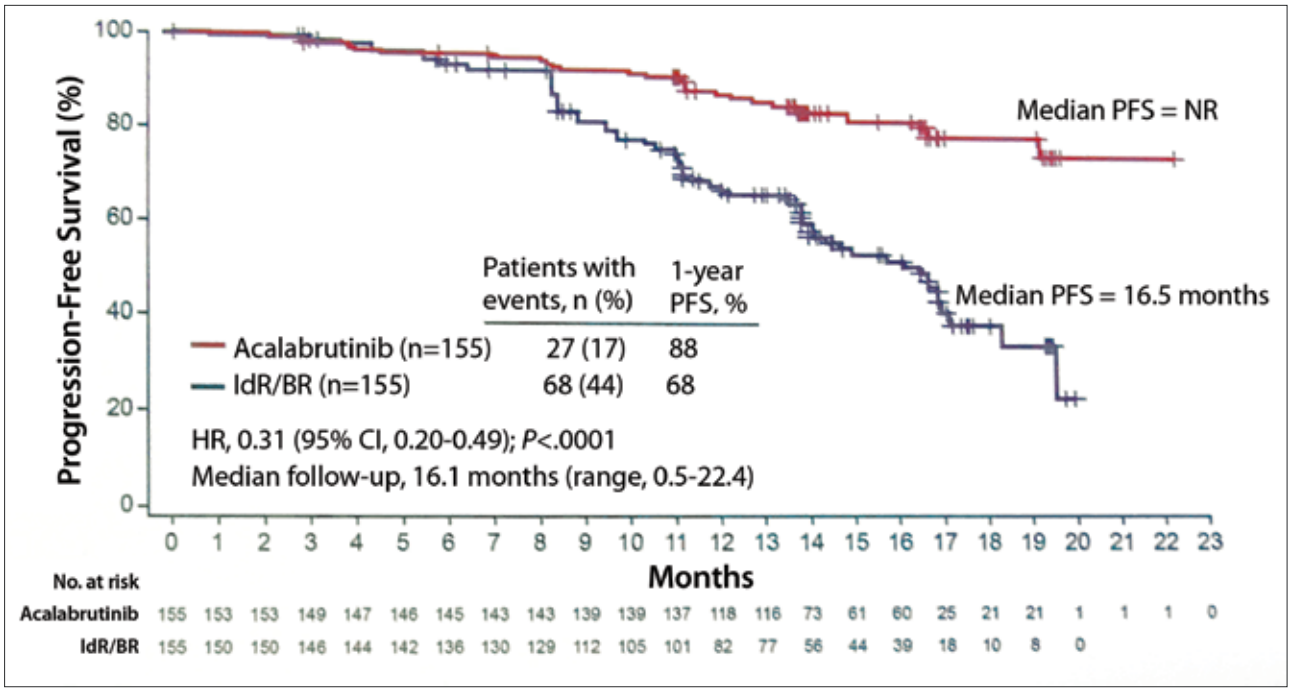

Figure 9. Median progression-free survival among patients in the phase 3 ASCEND trial. ASCEND, A Study of Acalabrutinib vs Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in R/R CLL. BR, bendamustine/rituximab; IdR, idelalisib/rituximab; NR, not reached. Adapted from Ghia P et al. Abstract 2158. Presented at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[3]

(70 mg/m^2, on days 1 and 2 of each cycle), based on the choice of their physician. Crossover into the acalabrutinib arm was allowed after confirmed disease progression. The primary endpoint was independently assessed PFS.

The trial randomly assigned 310 patients into the 2 arms. The patients' median age was 67.5 years (range, 32-90 years). Nearly half of patients (48.5%) had bulky disease, and 41.5% had Rai stage III/IV disease. In the acalabrutinib arm, patients had received a median of 1 prior therapy (range, 1-8). Genetic status in this arm included unmutated *IGHV* in 77%, complex karyotype in 32%, the 11q deletion in 25%, and the 17p deletion in 18%. In the control arms, patients had received a median of 2 prior therapies (range, 1-10). Genetic status included unmutated *IGHV* in 82%, complex karyotype in 30%, the 11q deletion in 29%, and the 17p deletion in 14%.

Based on independent review, the median PFS was not reached with acalabrutinib vs 16.5 months with the rituximab combinations (HR, 0.31; 95% CI, 0.20-0.49; *P*<.0001; Figure 9). Among patients with high-risk cytogenetics, the median PFS was not reached vs 16.2 months, respectively (HR, 0.27; 95% CI, 0.17-0.44; *P*<.0001). The PFS benefit seen with acalabrutinib was maintained across most patient subgroups, including those stratified by age, sex, Rai stage at screening, extent of bulky disease, and mutational status. PFS was better with the rituximab combinations among patients with an ECOG performance status of 2 at baseline and those who had received 4 or more therapies before study enrollment. Acalabrutinib demonstrated a superior response duration (HR, 0.33; 95% CI, 0.19-0.59; *P*<.0001). When PR with lymphocytosis was included in the analysis, the ORR was 88% with acalabrutinib vs 77% with the control regimens (*P*=.01). After excluding PR with lymphocytosis, the ORR did not differ significantly between the arms (*P*=.22).

The most common grade 3 or higher AEs associated with acalabrutinib included neutropenia (16%) and anemia (12%). Infections of any grade occurred in 56.5% of the acalabrutinib arm, vs 65.3 of the idelalisib/rituximab arm and 48.6% of the bendamustine/rituximab arm. Any-grade bleeding occurred in 26.0%, 8.0%, and 6.0%, respectively.

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Treatment of CLL From 2019 Onwards

Presentations at the XVIII iwCLL included several updates of trial data. The phase 3 E1912 trial compared ibrutinib plus rituximab, followed by maintenance ibrutinib, vs FCR in 529 patients ages 70 years and older with previously untreated CLL.[1,2] At a median follow-up of 48 months, 73% of patients remained on treatment. Among patients who stopped treatment with ibrutinib, median PFS was 22.5 months after discontinuation. PFS continued to show a benefit from treatment with ibrutinib plus rituximab compared with FCR (HR, 0.39; 95% CI, 0.26-0.57; *P*<.0001; Figure 10), with 3-year PFS rates of 89% vs 71%. PFS rates were similar with either treatment for patients with mutated *IGHV* (HR, 0.42; 95% CI, 0.16-1.16; *P*=.086). However, patients with unmutated *IGHV* benefited from treatment with ibrutinib plus rituximab compared with FCR (HR, 0.28; 95% CI, 0.17-0.48; *P*<.0001). OS was also superior with the ibrutinib combination (HR, 0.34; 95% CI, 0.15-0.79; *P*=.009).

The randomized phase 3 ALLIANCE (A041202) trial (Rituximab and Bendamustine Hydrochloride, Rituximab and Ibrutinib, or Ibrutinib Alone in Treating Older Patients With Previously Untreated Chronic Lymphocytic Leukemia) compared 3 treatment regimens: bendamustine plus rituximab, ibrutinib plus rituximab, and ibrutinib monotherapy. The trial enrolled 547 patients ages 65 years or older with previously untreated CLL.[3,4] The estimated rate of 2-year PFS was 88% with ibrutinib plus rituximab, 87% with ibrutinib, and 74% with bendamustine plus rituximab. At 52 months, the primary endpoint analysis showed superior PFS with both ibrutinib monotherapy (HR, 0.39; 95% CI, 0.26-0.58; *P*<.001) and ibrutinib plus rituximab (HR, 0.38; 95% CI, 0.25-0.59; *P*<.001) compared with bendamustine plus rituximab. There was no significant difference in PFS with ibrutinib monotherapy vs ibrutinib plus rituximab (*P*=.49). The trial included several subgroup analyses. Among the patients with a complex karyotype, the estimated 24-month PFS was 91% with ibrutinib, 87% with ibrutinib/rituximab, and 59% with bendamustine plus rituximab. Patients with the 17p deletion and unmutated *IGHV* also benefited from ibrutinib alone or ibrutinib plus rituximab vs bendamustine/rituximab. Two-year OS was similar for all 3 treatment cohorts, at 95% with bendamustine plus rituximab, 94% with ibrutinib plus rituximab, and 90% with ibrutinib (*P*≥.65). At a median follow-up of 38 months, the rates of grade 3/4 hematologic AEs were higher with bendamustine plus rituximab (61%) vs ibrutinib monotherapy (41%) or ibrutinib plus rituximab (39%; *P*<.001). Rates of grade 3/4 nonhematologic AEs were higher in the 2 ibrutinib arms (74%) compared with bendamustine/rituximab (63%; *P*=.04).

The phase 3 ILLUMINATE trial (A Multi-Center Study of Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Patients With Treatment Naïve CLL or SLL) compared ibrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab in 229 patients with treatment-naive CLL/SLL.[5,6] At a median follow-up of 31.3 months (range, 0.2-36.9 months), the median PFS was not reached with the ibrutinib combination vs 19.0 months with the chlorambucil combination (HR, 0.231; 95% CI, 0.145-0.367; *P*<.0001). Among the patients with high-risk genetic

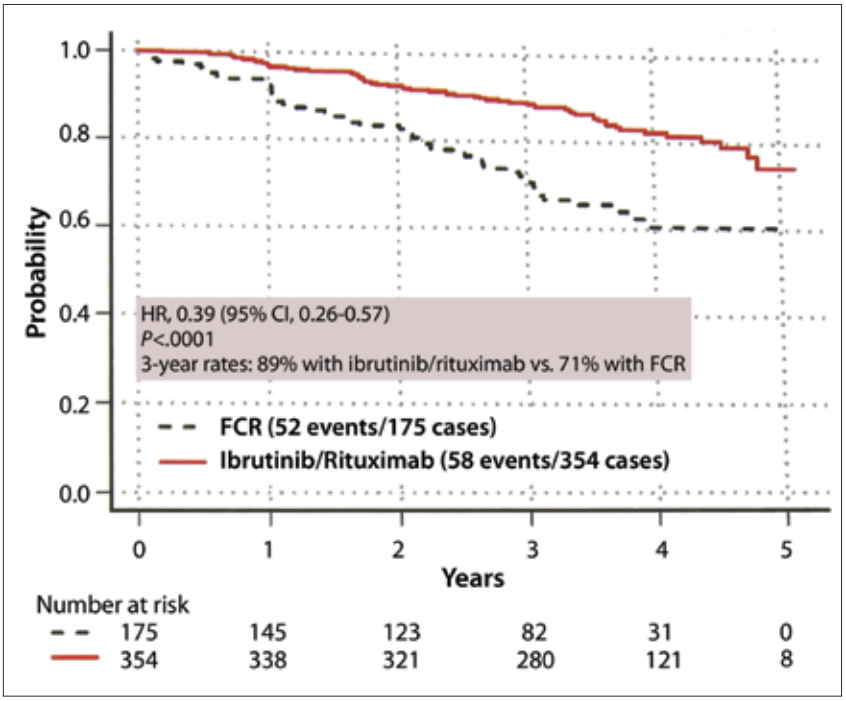

Figure 10. Progression-free survival in a 3-year analysis of the phase 3 E1912 trial. FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio. Adapted from Shanafelt TD. Treatment of CLL from 2019 onwards: E1912 trial. Presentation at: the XVIII International Workshop on CLL; September 20-23, 2019; Edinburgh, Scotland.[1]

features, median PFS was not reached with ibrutinib plus obinutuzumab vs 14.7% with chlorambucil plus obinutuzumab (HR, 0.154; 95% CI, 0.087-0.270; *P*<.0001). Nearly all subgroups benefited from treatment with ibrutinib vs chlorambucil. ORR was 88% with ibrutinib plus obinutuzumab vs 73% with chlorambucil plus obinutuzumab. The rates of CR/incomplete CR were 19% vs 8%, respectively. Patients in the ibrutinib arm also had higher rates of undetectable MRD. The safety profile of ibrutinib plus obinutuzumab was consistent with the known AE profiles of the individual agents.

The phase 3 CLL14 trial randomly assigned 432 patients with CLL and coexisting medical conditions to receive fixed-duration venetoclax plus obinutuzumab or chlorambucil plus obinutuzumab as first-line therapy.[7,8] Treatment consisted of 6 cycles of combination therapy followed by 6 cycles of venetoclax or chlorambucil monotherapy. After a median of 38 months of follow-up, the median PFS was significantly prolonged with the venetoclax combination (HR, 0.35; 95% CI, 0.23-0.53; *P*<.0001). The proportion of patients with negative ($<10^{-4}$) MRD status was higher with venetoclax plus obinutuzumab compared with chlorambucil plus obinutuzumab, reaching 76% vs 35% (*P*<.001) with peripheral blood testing and 57% vs 17% (*P*<.001) with bone marrow testing.

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Highlights From the XVIII International Workshop on Chronic Lymphocytic Leukemia: Commentary

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Study presentations at the XVIII International Workshop on Chronic Lymphocytic Leukemia (iwCLL) provided interesting new data. In addition, there were long-term follow-up analyses for several important clinical trials. Studies evaluated treatments such as ibrutinib, acalabrutinib, and venetoclax plus rituximab.

Ibrutinib

Dr Petra Langerbeins and colleagues presented preliminary results of the randomized, phase 3 German CLL12 trial (Ibrutinib in Previously Untreated Binet Stage A Chronic Lymphocytic Leukemia With Risk of Disease Progression), which compared ibrutinib vs placebo among patients with asymptomatic, treatment-naive, early-stage CLL.[1] This trial examined the important question of whether early treatment of CLL can be beneficial. This question is not yet answered by these preliminary results.

Approximately 80% of patients with CLL have asymptomatic, early-stage disease. Although the standard approach to these patients is watch and wait, the value of this strategy is unknown. In general, the paradigm in cancer is that the best chance of curing a disease is to catch it early and administer treatment. With the watch-and-wait approach, the disease might progress and develop more molecular abnormalities. When treatment is initiated, it then leads to a small cure fraction limited to young, fit patients who can tolerate treatment with fludarabine, cyclophosphamide, and rituximab (FCR).[2]

In the 1980s, several randomized trials in patients with early-stage, asymptomatic CLL compared watch

and wait vs immediate treatment with chlorambucil.[3] These trials consistently showed no benefit to early treatment with chlorambucil. Currently, however, there are far more effective therapies than chlorambucil, such as ibrutinib.[4] However, it is known that approximately one-third of patients with CLL will never need treatment. Therefore, a more effective clinical trial design would limit enrollment to high-risk patients with disease that will ultimately progress and require treatment. The CLL12 trial enrolled patients with Binet stage A, which is equivalent to Rai stage 0 to 1.[1] The standard approach for these asymptomatic, treatment-naive patients is watch and wait. The CLL12 trial stratified patients according to a previously published German criteria that identified low, intermediate, high, or very high risk.[5] The 152 patients with low-risk disease were assigned to the watch-and-wait arm. The remaining 363 patients—those at intermediate, high, or very high risk—were randomly assigned to treatment with ibrutinib (n=182) or placebo (n=181). The study combined these risk levels into one group based on relatively small numbers of patients with high-risk (n=82) or very high-risk (8) disease. Ideally, it would have been preferable to enroll only patients at high or very high risk, but a population of 90 would have been challenging for a randomized trial. A limitation to the CLL12 trial is the heterogeneous enrollment. However, the ibrutinib arm and the placebo arm were well matched in terms of age, performance status, and comorbidity scores, as assessed by the Cumulative Illness Rating Scale (CIRS).

The rates of any-grade adverse events (AEs) were 94.9% in the ibrutinib arm and 95.5% in the placebo arm. The rate of AEs in the placebo arm highlights the fact that many AEs reported in a clinical trial are not, in fact, related to treatment, but rather to the underlying disease. Grade 3 or higher AEs were reported in 50.6% of the ibrutinib arm and 43.2% of the placebo arm. A difference between the arms is seen among AEs leading to interruption. For example, 18 patients in the ibrutinib arm discontinued treatment owing to arrhythmias, whereas none did so in the placebo arm. Bleeding led to treatment discontinuation among 8 patients in the ibrutinib arm vs 1 in the placebo arm. Infections required 3 patients to stop ibrutinib and 4 patients to stop placebo. Therefore, the biggest difference in AEs was arrhythmias leading to discontinuation in the ibrutinib arm. It is known that ibrutinib can cause atrial fibrillation and, occasionally, ventricular arrhythmias, as well as bleeding. There were no treatment-related fatal adverse events in either arm.

The study also provided data on AEs of clinical interest.[1] Rates of grade 3 or higher diarrhea were 1.3% with ibrutinib and 3.2% with placebo. These rates show that throughout a follow-up duration of 18 months, some patients will develop diarrhea that has nothing to do with treatment. It is known that bleeding can be related to ibrutinib. Grade 3 or higher bleeding was reported in 3.8% of the ibrutinib arm vs 1.2% of the placebo arm. All-grade atrial fibrillation occurred in 20.9% of the ibrutinib arm vs 7.7% of the placebo arm. Grade 3 or higher events occurred in 7.6% vs 1.3%, respectively. All-grade hypertension, another known side effect of ibrutinib, occurred in 11.4% vs 4.5%. Grade 3 or higher hypertension was reported in 1.9% of patients in both groups. Therefore, severe toxicities in the ibrutinib arm consisted of a small proportion of AEs overall.

The presentation by Dr Langerbeins provided data for the time to symptomatic progression.[1] Among patients treated with ibrutinib, the median time to symptomatic progression was not reached. Not surprisingly, patients in the placebo arm developed slowly progressive disease, with a median time to symptomatic progression of approximately 4 years. (It should be mentioned that progression does not always signal a need for therapy.) This finding shows that these patients as a group were not at very high risk.

The more important endpoint is survival. An analysis of progression-free survival (PFS) showed that events occurred in 30 patients treated with ibrutinib vs 101 patients treated with placebo. The median PFS was 14.8 months with placebo vs not reached with ibrutinib (hazard ratio, 0.176; $P<.0001$). However, thus far there is no difference in overall survival. Therefore, the results at this point will probably not change clinical practice. The important issue is whether earlier treatment will improve survival, and it is too early to know based on this report. As just discussed, even with a very effective therapy like ibrutinib, there are side effects. For example, arrhythmias are a significant side effect that can occur with ibrutinib. It will be important to confirm the benefits of early treatment before this strategy enters clinical practice.

Dr Alessandra Tedeschi and colleagues presented long-term follow-up data from the RESONATE-2 trial (Open-Label Phase 3 BTK Inhibitor Ibrutinib vs Chlorambucil in Patients 65 Years or Older With Treatment-Naive CLL or SLL).[6] RESONATE-2 was the first randomized trial of ibrutinib in the frontline setting. The trial randomly assigned older patients who required therapy to ibrutinib or chlorambucil.[4] Most patients were older than 69 years; patients ages 65 to 69 years could be enrolled if they had a comorbidity that precluded FCR. The patients' median age was approximately 73 years, which reflects the trial's aim of selecting an older cohort with significant comorbidities, which is reasonable because the control arm consisted of chlorambucil, a mild chemotherapy. Approximately one-third of the patients had a comorbidity score higher than 6. The trial did not enroll patients with the 17p deletion, who do not benefit from chemotherapy. The primary endpoint was PFS.

Dr Tedeschi presented results from the 5-year analysis, which represents the longest follow-up data for a randomized clinical trial of ibrutinib in the frontline setting.[6] The rate of complete response was 30% among patients treated with ibrutinib, increasing from 11% at the primary analysis. Impressively, the median PFS was still not reached in the ibrutinib arm. As previously reported, the median PFS for chlorambucil was 15 months. At 5 years, the estimated rates of PFS were 70% in the ibrutinib arm vs 12% in the chlorambucil arm. The estimated rates of overall survival at 5 years were 83% with ibrutinib vs 68% with chlorambucil. The improvement in overall survival is particularly impressive given that patients who developed progressive disease during treatment with chlorambucil were allowed to cross over to the ibrutinib arm when they met iwCLL criteria for further therapy. These data show that frontline remissions are durable with continued ibrutinib.

The study found an interesting outcome for patients with the 11q deletion. It is known that this mutation is associated with a lower PFS in response to any type of chemotherapy, and results in the chlorambucil arm of RESONATE-2 confirmed this earlier observation.[4] In the ibrutinib arm, however, the presence of the 11q deletion did not worsen PFS. In fact, there was a benefit to PFS, albeit that lacked statistical significance, among patients with the mutation receiving ibrutinib. Similarly, it is known that patients with the immunoglobulin heavy chain gene (*IGHV*) mutation have a shorter PFS in response to chemotherapy. In RESONATE-2, patients with this mutation had a worse response to chlorambucil, but not to ibrutinib. No difference in PFS was observed based on *IGHV* status in the ibrutinib arm.

Acalabrutinib

Dr Wojciech Jurczak and coworkers presented results of the ASCEND trial (A Study of Acalabrutinib vs Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in R/R CLL), which will likely lead to the FDA approval of acalabrutinib for patients with CLL.[7] Acalabrutinib is already approved for mantle cell lymphoma, but not yet for any other disease. Compared with ibrutinib, acalabrutinib is a more-selective BTK inhibitor and has less off-target kinase inhibition.[8] Acalabrutinib has a higher half maximal inhibitory concentration (IC_{50}) for some of the kinases that lead to the side effects seen with ibrutinib (eg, atrial fibrillation). ASCEND was a global, multicenter, randomized phase 3 trial that enrolled 310 patients with relapsed CLL. The trial consisted of 3 arms: acalabrutinib, idelalisib plus rituximab, and bendamustine plus rituximab. The dose of acalabrutinib was 100 mg twice daily. (In contrast, ibrutinib is administered once daily.) The other treatments were administered at the standard doses. The selection of the control arm was made by the investigator. The primary endpoint was PFS.

The patient characteristics were well matched between the treatment and control arms. The population was not heavily pretreated. Patients in the acalabrutinib arm had received a median of 1 prior therapy, and those in the control arms had received a median of 2.

Median PFS was not reached in the acalabrutinib arm vs 16.5 months for patients treated with idelalisib/rituximab or bendamustine/rituximab combined.[7] Rates of 1-year PFS were 88% with acalabrutinib vs 68% among patients in the control arms. Outcomes were similar between the 2 control arms. This trial had an independent review committee, which verified the findings. The overall response rate was high in all of the arms, at 81% with acalabrutinib and 76% in the control arms. There were only 2 complete responses, both reported in the control arms. At a median follow-up of 16 months, the survival curves were overlapping.

Acalabrutinib was generally well tolerated. Some differences were noted regarding toxicities. There was more neutropenia with either idelalisib/rituximab (45%) or bendamustine/rituximab (34%) than with acalabrutinib (19%). Diarrhea was significantly more common with idelalisib/rituximab (47%) vs bendamustine/rituximab (14%) or acalabrutinib (18%). The incidence of atrial fibrillation was 5% in the acalabrutinib arm vs 3% in the control arms. Hypertension occurred in 3% of the acalabrutinib arm, 3% of the idelalisib/rituximab arm, and 0% of the bendamustine/rituximab arm. Bleeding occurred in 26%, 8%, and 6%, respectively, and most events were minor. Rates of grade 3 or higher bleeding were similar among the arms.

Venetoclax Plus Rituximab

The randomized, open-label phase 3 MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL]) led to the FDA approval of venetoclax and rituximab for patients with relapsed CLL. Results from this trial were published by Dr John Seymour and colleagues in the *New England Journal of Medicine*,[9] and updated with 3-year follow-up at the 60th American Society of Hematology (ASH) annual meeting.[10] A report at the iwCLL meeting provided 4-year follow-up.[11] The MURANO trial compared venetoclax/rituximab vs bendamustine/rituximab. Importantly, this trial is among the first to evaluate a time-limited regimen of a small molecule therapy. When venetoclax was approved as a single agent, the indication encompassed an indefinite, continuous administration regimen, as is used for ibrutinib. In the MURANO trial, the investigational regimen consisted of venetoclax and rituximab given for the first 6 months, followed by venetoclax alone for the next 18 months.

With a median follow-up of approximately 4 years, the median time off therapy was approximately 2 years. The estimated rates of 4-year PFS were 57% with venetoclax/rituximab vs 4.6% with bendamustine/rituximab. The median PFS was not yet reached with venetoclax/rituximab vs approximately 16 months with bendamustine/rituximab.[10]

The MURANO trial included several subanalyses of patients based on genetic mutations and molecular abnormalities. Among patients treated with venetoclax/rituximab, the 3-year PFS was 76% in those without the 17p deletion vs 64% in those with the deletion.[10] Presence of the *TP53* mutation did not impact 3-year PFS among patients treated with venetoclax/rituximab. In the bendamustine/rituximab arm, PFS was shorter among patients with a *TP53* mutation. Data verify that patients with a 17p deletion or *TP53* mutation generally should not be treated with chemotherapy.[12-14] Mutations in the ataxia telangiectasia mutated (*ATM*) gene or the neurogenic locus notch homolog protein 1 (*NOTCH1*) gene did not appear to greatly impact outcome in either arm. The study defined high-genomic complexity as more than 5 aberrations on cytogenetic analysis. In this group of patients, PFS was shorter in both treatment arms. The 4-year analysis showed a continued improvement in survival with venetoclax/rituximab, although this trial did not allow crossover.

The study assessed minimal residual disease (MRD) and categorized results as undetectable, low-positive, or high-positive. Relapse appeared to closely correlate with positive MRD status at the end of therapy. At the end of 2 years of treatment with venetoclax/rituximab, 83 patients were undetectable for MRD. Only 11 of these patients had developed progressive disease by the 4-year follow-up analysis. Among the 23 patients who were low MRD positive at the end of therapy, 9 progressed (39%). Among the 14 patients who were high MRD positive, 13 progressed (93%). It is known that patients with high MRD positive values are more likely to have the 17p deletion or *TP53* mutation. Although these patients had better outcomes with venetoclax/rituximab vs chemotherapy, their outcomes were still inferior to those without the 17p deletion or *TP53* mutation.

At the 60th ASH meeting, the question was raised regarding whether extending therapy beyond 2 years might have allowed patients who were high MRD positive to become MRD negative. Interestingly, Dr Seymour did not think so.[10] During the trial, MRD was assessed at several time points before the 2-year mark. Dr Seymour noted that for most of those patients, levels of MRD had already reached a plateau or were actually increasing. He expressed doubts that the refractory group would have become MRD negative with continued therapy. A further question is whether continued therapy might lead to prolonged remission among patients who remained MRD positive.

Disclosure

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