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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 60th American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 60th American Society of Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

Special Reporting on:

- Ibrutinib Alone or in Combination With Rituximab Produces Superior Progression-Free Survival Compared With Bendamustine Plus Rituximab in Untreated Older Patients With Chronic Lymphocytic Leukemia: Results of Alliance North American Intergroup Study A041202
- A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients With Chronic Lymphocytic Leukemia: A Trial of the ECOG-ACRIN Cancer Research Group (E1912)
- MURANO Trial Establishes Feasibility of Time-Limited Venetoclax-Rituximab Combination Therapy in Relapsed/Refractory Chronic Lymphocytic Leukemia
- Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma: Results From Phase 3 iLLUMINATE
- Comparison of Efficacy and Toxicity of CD19-Specific Chimeric Antigen Receptor T Cells Alone or in Combination With Ibrutinib for Relapsed and/or Refractory CLL
- A Phase II Trial of Nivolumab Combined With Ibrutinib for Patients With Richter Transformation

PLUS Meeting Abstract Summaries

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#1 PRESCRIBED THERAPY IN FRONTLINE† AND PREVIOUSLY TREATED CLL‡[1]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA® (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS[2]

†Based on market share data from IMS from November 2016 to February 2018.
‡Based on market share data from IMS from July 2014 to February 2018.

CLL
SLL

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

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

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

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

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 1,011 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 1,011 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 has occurred in 12% of 1,011 patients treated with IMBRUVICA® in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 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.

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RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3] Patients with 17p deletion were excluded[3]

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

Statistically significant reduction in risk of death **56%**
HR=0.44 (95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA® upon disease progression

Estimated survival rates at 24 months

IMBRUVICA® **95%** (95% CI: 89, 97)

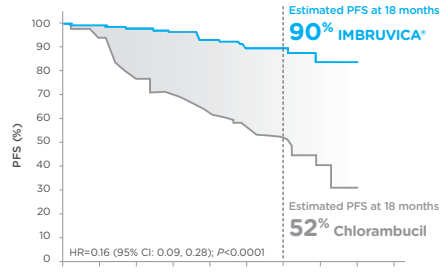
chlorambucil **84%** (95% CI: 77, 90)

- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not estimable vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain (36%)
- Cough (22%)
- Rash (21%)
- Bruising (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection (15%)

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%)*, neutropenia (58%)*, diarrhea (42%), anemia (39%)*, rash (31%), musculoskeletal pain (31%), bruising (31%), nausea (28%), fatigue (27%), hemorrhage (23%), 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 (36%)*, thrombocytopenia (15%)*, and pneumonia (10%).

Approximately 7% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included hemorrhage (1.2%), atrial fibrillation (1.0%), pneumonia (1.0%), rash (0.7%), diarrhea (0.6%), neutropenia (0.6%), sepsis (0.5%), interstitial lung disease (0.3%), bruising (0.2%), non-melanoma skin cancer (0.2%), and thrombocytopenia (0.2%). Eight percent of patients had a dose reduction due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

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.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, iwCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2018. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

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

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

INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,011 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 1,011 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 has occurred in 12% of 1,011 patients treated with IMBRUVICA in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 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 adverse reactions are discussed in more detail in other sections of the labeling:

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 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.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
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

Table 3: 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 4 (%)
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

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

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

RESONATE: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

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

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
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

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

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given 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

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

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

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2 (continued)

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

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

HELIOS: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
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

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS (continued)

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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%

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.

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

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

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

Study 1118 and INNOVATE Monotherapy Arm: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

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

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Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

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

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

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

INNOVATE: Adverse reactions described below in Table 11 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 11: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

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

Table 11: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE (continued)

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and Lymphatic System Disorders				
Neutropenia*	16	12	11	4
Cardiac Disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

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

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

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 12 and 13 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 12: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2

Table 12: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

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

Table 13: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

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

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

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

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

Adverse reactions and laboratory abnormalities described below in Tables 14 and 15 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 14: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

Table 15: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

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

Additional Important Adverse Reactions: *Cardiac Arrhythmias:* In randomized controlled trials (n=1377; median treatment duration of 14.0 months for patients treated with IMBRUVICA and 7.5 months for 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 0.4% 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 8% versus 2% and for Grade 3 or greater was 4% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: Diarrhea of any grade occurred at a rate of 40% of patients treated with IMBRUVICA compared to 19% 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 475) versus 47 days (range: 0 to 492) for any grade diarrhea and 77 days (range: 3 to 310) 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, 84% versus 88% had complete resolution, and 16% versus 12% 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 6 days (range: 1 to 655) versus 5 days (range: 1 to 367) for any grade diarrhea and 6 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: Blurred vision and decreased visual acuity of any grade occurred in 12% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 96 days (range, 0 to 617) versus 109 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 61% versus 71% had complete resolution and 39% 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 31 days (range, 1 to 457) versus 29 days (range, 1 to 253) 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

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].*

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Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information].*

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

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

USE IN SPECIFIC POPULATIONS

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

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

Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, 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:* Verify the pregnancy status of 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. Pediatric studies have not been completed.

Geriatric Use: Of the 1011 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 22% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

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

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

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

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].*
- 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].*
- 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-04482

Ibrutinib Alone or in Combination With Rituximab Produces Superior Progression-Free Survival Compared With Bendamustine Plus Rituximab in Untreated Older Patients With Chronic Lymphocytic Leukemia: Results of Alliance North American Intergroup Study A041202

The randomized phase 3 RESONATE-2 trial (Open-Label Phase 3 BTK Inhibitor Ibrutinib vs Chlorambucil in Patients 65 Years or Older With Treatment-Naive CLL or SLL) compared ibrutinib vs chlorambucil as first-line therapy in older patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[1,2] After stratification according to Eastern Cooperative Oncology Group (ECOG) performance status and Rai disease stage, 269 patients were randomly assigned into each arm. The trial met its primary endpoint, demonstrating a median progression-free survival (PFS) that was not reached in the ibrutinib arm vs 15 months in the chlorambucil arm (hazard ratio [HR], 0.121; 95% CI, 0.074-0.198; *P*<.0001). The estimated 24-month overall survival (OS) was 95% with ibrutinib vs 84% with chlorambucil. The findings led to regulatory approval of ibrutinib as first-line treatment in this setting. A single-center trial evaluated ibrutinib with or without rituximab in patients with CLL.[3] The study enrolled 181 patients with relapsed CLL and 27 treatment-naive patients with high-risk disease. After a median follow-up of 36 months, the estimated PFS rates were 86.0% for patients treated with ibrutinib alone vs 86.9% for patients who also received rituximab.

At the Plenary Session of the 60th American Society of Hematology (ASH) meeting, Dr Jennifer Woyach presented results from the Alliance North American Intergroup Study A041202 (Rituximab and Bendamustine Hydrochloride, Rituximab and Ibrutinib, or Ibrutinib Alone in Treating Older Patients With Previously Untreated Chronic Lymphocytic Leukemia), a phase 3 trial that evaluated the efficacy and safety of ibrutinib monotherapy, ibrutinib plus rituximab, and bendamustine plus rituximab in elderly patients with treatment-naive CLL.[4,5] Eligible patients were ages 65 years or older, required treatment for CLL, and had an ECOG performance status of 0 to 2.[6] After randomization for disease risk, chromosomal deletion, and degree of Zap70 methylation, patients were randomly assigned into the 3 treatment arms. In the bendamustine/rituximab arm, the dose of bendamustine was 90 mg/m^2 on days 1 and 2, and the dose of rituximab was 375 mg/m^2 on day 0 of cycle 1, then 500 mg/m^2 on day 1 of cycles 2 through 6. In the monotherapy arm, the dose of ibrutinib was 420 mg daily. Patients in the ibrutinib/rituximab arm received 420 mg of ibrutinib plus rituximab at 375 mg/m^2 weekly for 4 weeks starting on day 1 of cycle 2, then 375 mg/m^2 on day 1 of cycles 3 through 6. Patients enrolled in the bendamustine/rituximab arm who progressed and required therapy could cross over to the ibrutinib arm. The primary endpoint was PFS.

The 547 enrolled patients had a median age of 71 years (range, 65-89 years), and two-thirds were male. Ninety-seven percent of the patients had an ECOG performance status of 0 or 1, and the median white blood cell count was 82 × 10^3/µL. Genomic aberrations included unmutated immunoglobulin heavy chain variable (*IGHV*; 61%), unmethylated Zap70 (53%), the complex karyotype (29%), the *TP53* mutation (10%), deletion of chromosome 11q (19%), and deletion of chromosome 17p (6%). Seventy-four percent of eligible patients participated in a Geriatric Assessment Correlative Study. No significant

ABSTRACT SUMMARY: Ibrutinib Plus Venetoclax in Relapsed/Refractory CLL: Results of the Bloodwise TAP CLARITY Study

The phase 2 CLARITY study (Venetoclax and Ibrutinib in Treating Patients With Chronic or Small Lymphocytic Leukemia) investigated the safety and efficacy of ibrutinib plus venetoclax in patients with previously treated CLL (Abstract 182). Enrolled patients received daily venetoclax (400 mg) plus ibrutinib (420 mg). The study enrolled 54 patients with a median age of 64 years (range, 31-83 years) and a median of 1 prior treatment (range, 1-6). The ORR was 94%. At month 14, the rates of undetectable MRD were 57% according to peripheral blood analysis and 39% according to bone marrow analysis. Among patients who had relapsed within 36 months of chemoimmunotherapy, these rates were 70% vs 45%. Among 25 patients treated for 24 months, 9 (36%) achieved less than .001% leukemic cells in the bone marrow. Treatment was generally well-tolerated. The majority of AEs were minor. One case of grade 3 laboratory tumor lysis syndrome occurred.

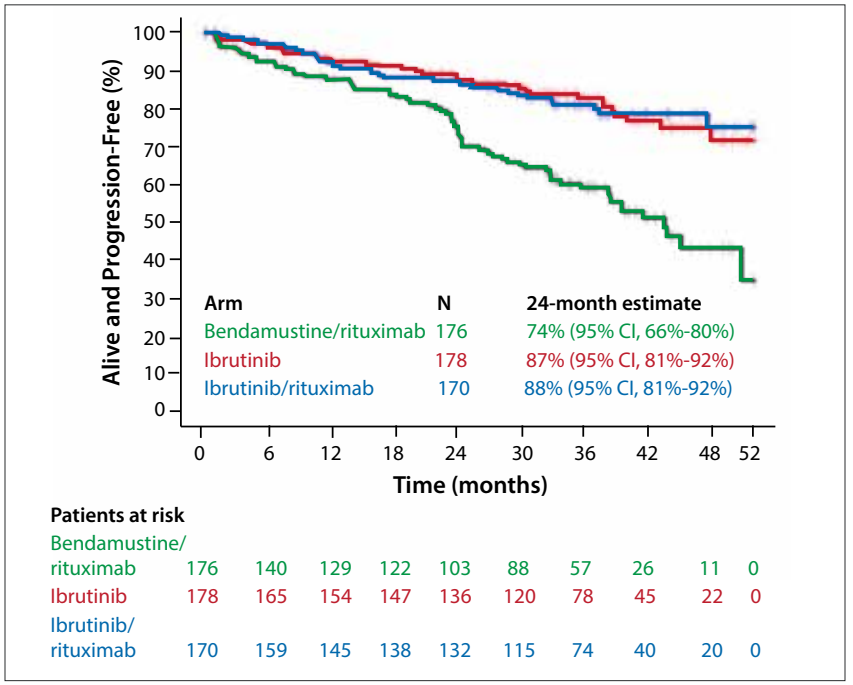

Figure 1. The primary endpoint of progression-free survival in Study A041202 from the Alliance North American Intergroup, which evaluated bendamustine plus rituximab, ibrutinib monotherapy, and ibrutinib plus rituximab as frontline treatment. Adapted from Woyach JA et al. ASH abstract 6. *Blood*. 2018;132(suppl 1).[4]

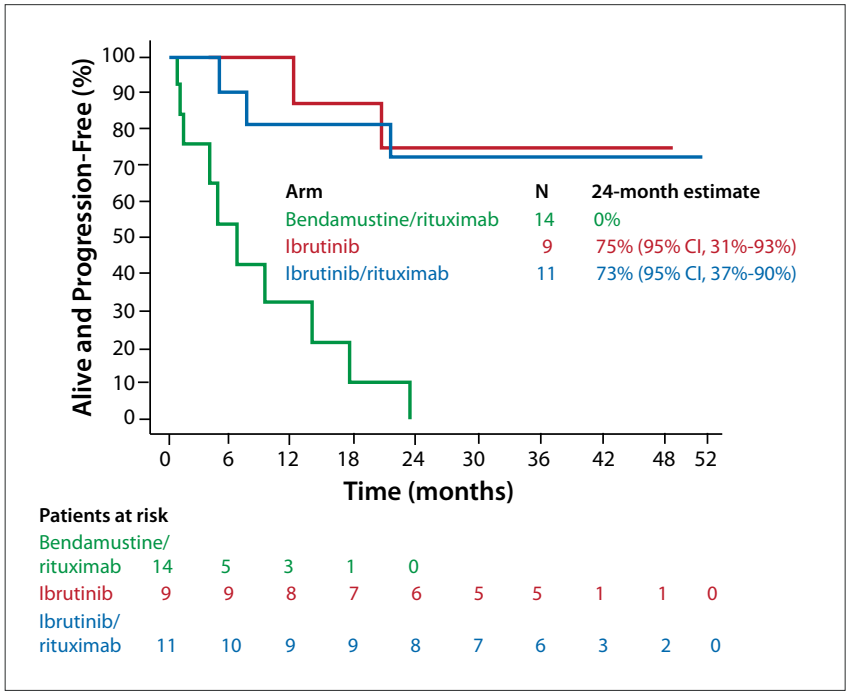

Figure 2. Progression-free survival among patients with deletion 17p13.1 in Study A041202 from the Alliance North American Intergroup, which evaluated bendamustine plus rituximab, ibrutinib monotherapy, and ibrutinib plus rituximab as frontline treatment. Adapted from Woyach JA et al. ASH abstract 6. *Blood*. 2018;132(suppl 1).[4]

differences emerged among the 3 treatment arms at baseline, based on scores for activities of daily living (mean, 13.7), number of coexisting conditions (mean, 2.5), and falling at least once in the prior 6 months (12.7%).

Ibrutinib with or without rituximab demonstrated a superior PFS compared with bendamustine plus rituximab. The estimated PFS at 24 months was 74% (95% CI, 66%-80%) with bendamustine plus rituximab, 87% (95% CI, 81%-92%) with ibrutinib monotherapy, and 88% (95% CI, 81%-92%) with ibrutinib plus rituximab (Figure 1). Compared with bendamustine plus rituximab, the HR for PFS was 0.39 (95% CI, 0.26-0.58; *P*<.001) with ibrutinib monotherapy and 0.38 (95% CI, 0.25-0.59; *P*<.001) with ibrutinib plus rituximab. Comparison of ibrutinib plus rituximab vs ibrutinib monotherapy yielded an HR of 1.00 (95% CI, 0.62-1.62; *P*=.49). Patients with deletion of 17p13.1 had an estimated 24-month PFS of 75% (95% CI, 31%-93%) with ibrutinib monotherapy and of 73% (95% CI, 37%-90%) with ibrutinib plus rituximab, vs 0% with bendamustine plus rituximab (Figure 2). Among patients with the complex karyotype, the estimated 24-month PFS was also superior with ibrutinib monotherapy (91%; 95% CI, 75%-97%) or ibrutinib plus rituximab (87%; 95% CI, 75%-94%) vs bendamustine plus rituximab (59%; 95% CI, 42%-73%). The overall response rates (ORRs) were 93% (95% CI, 88%-96%) with ibrutinib monotherapy, 94% (95% CI, 89%-97%) with ibrutinib plus rituximab, and 81% (95% CI, 75%-87%) with bendamustine plus rituximab.

Complete responses (CRs) were seen in 26% of the bendamustine/rituximab arm (95% CI, 20%-33%), 12% of the ibrutinib/rituximab arm (95% CI, 8%-18%), and 7% of the ibrutinib monotherapy arm (95% CI, 4%-12%). Dr Woyach noted that responses achieved with ibrutinib tend to deepen over time, and the CR rate

may increase in the ibrutinib arms. Minimal residual disease (MRD) in the bone marrow was negative at 9 months in 8% (95% CI, 5%-13%) of patients receiving bendamustine plus rituximab, 4% (95% CI, 2%-8%) of those treated with ibrutinib plus rituximab, and 1% (95% CI, <1%-3%) of those receiving ibrutinib monotherapy. After a median follow-up of 38 months, the estimated 24-month OS was similar for the 3 arms, at 95% with bendamustine plus rituximab (95% CI, 91%-98%), 90% with ibrutinib monotherapy (95% CI, 85%-94%), and 94% with ibrutinib plus rituximab (95% CI, 89%-97%).

Grade 3, 4, or 5 hematologic toxicities occurred in 61% of the bendamustine/rituximab arm, 41% of the ibrutinib monotherapy arm, and 38% of the ibrutinib/rituximab arm (P<.001). Grade 3, 4, or 5 nonhematologic toxicities occurred in 63%, 74%, and 74% (P=.04), respectively.

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A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients With Chronic Lymphocytic Leukemia: A Trial of the ECOG-ACRIN Cancer Research Group (E1912)

The treatment landscape for patients with CLL or SLL has changed dramatically in the past several years.[1] The development of chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) improved PFS and OS compared with chemotherapy alone and is the first-line standard of care for CLL patients who are younger than 65 years and who do not have comorbidities.[2] Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase (BTK), which mediates B-cell receptor signaling. Treatment with ibrutinib has led to durable responses and improved survival in patients with relapsed or refractory CLL and in older patients who are treatment-naive.[3,4]

In the Late-Breaking Abstract session of the 60th ASH meeting, Dr Tait Shanafelt presented results from the ECOG/American College of Radiology Imaging Network (ACRIN) group phase 3 E1912 trial (Ibrutinib and Rituximab Compared With Fludarabine Phosphate, Cyclophosphamide, and Rituximab in Treating Patients With Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma), which compared ibrutinib plus rituximab vs FCR in young patients who were treatment-naive.[5] Eligible patients were ages 70 years or younger, did not harbor the chromosome 17p deletion, had adequate creatinine clearance, and required treatment based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 recommendations.[6] Prior to randomization, patients were stratified based on age, performance status, disease stage, and status of chromosome 11q22.3 (ataxia telangiectasia mutated). Patients were randomly assigned 2:1 to receive ibrutinib (420 mg daily) or 6 courses of intravenous fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) on days 1 through 3 every 28 days. All patients also received rituximab (50 mg/m^2 on day 1, then 325 mg/m^2 on day 2, followed by 500 mg/m^2 on day 1 of subsequent cycles). Rituximab was administered during cycles 1 to 6 for patients in the FCR arm and during cycles 2 through 7 in the ibrutinib/rituximab arm. Patients in the ibrutinib/rituximab arm continued to receive daily ibrutinib (420 mg) after completion of 7 cycles of ibrutinib plus rituximab. The primary endpoint was PFS, with a secondary endpoint of OS. All randomized patients were included in the primary analysis.

The study randomly assigned 354 patients to ibrutinib plus rituximab and 175 to FCR. Patient characteristics were well-balanced between the

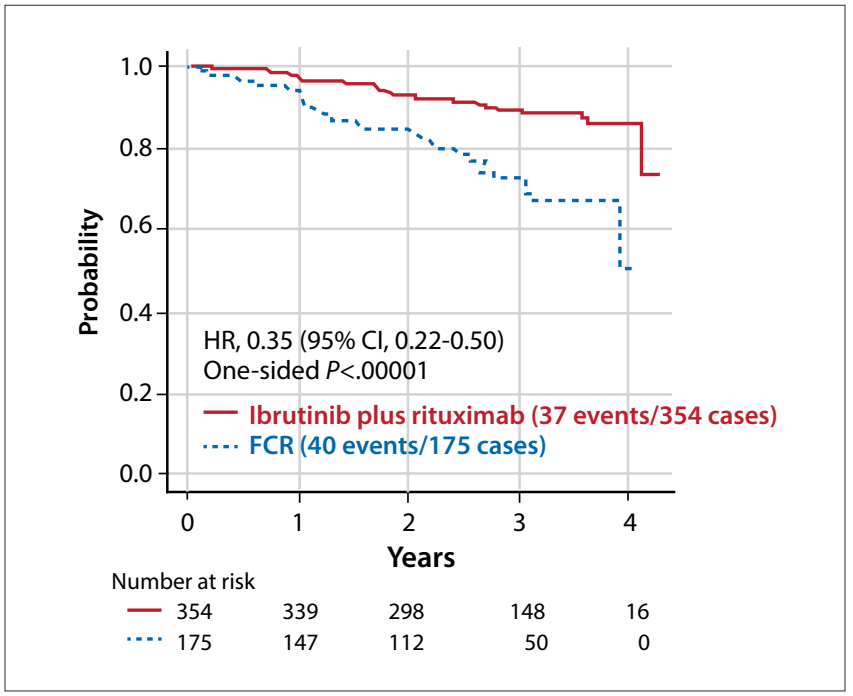

Figure 3. In the intention-to-treat analysis of the phase 3 E1912 trial, progression-free survival was superior with ibrutinib plus rituximab vs FCR among treatment-naive patients. E1912, Ibrutinib and Rituximab Compared With Fludarabine Phosphate, Cyclophosphamide, and Rituximab in Treating Patients With Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio. Adapted from Shanafelt TD et al. ASH abstract LBA-4. *Blood*. 2018;132(suppl 1).[5]

ABSTRACT SUMMARY: Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for First-Line Treatment of Patients With CLL With Mutated *IGHV* and Without *TP53* Aberrations

An investigator-initiated phase 2 trial evaluated ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) in treatment-naive CLL patients with mutated *IGHV* and without the chromosome 17p deletion or *TP53* mutation (Abstract 185). The primary endpoint was CR/CRi with undetectable MRD at 10^{-4} sensitivity in the bone marrow after 3 cycles of therapy. Depending on the patient's response, obinutuzumab was continued for up to 9 cycles and ibrutinib for up to 12 cycles. After a median follow-up of 22.3 months (range, 3.5-32.1 months), 44 patients had an ORR of 100%, including 39% with a CR/CRi, and 39 patients (89%) had undetectable bone marrow MRD. Among 32 patients with 1 year of follow-up, 100% had undetectable bone marrow MRD and had discontinued ibrutinib. No patient had MRD or clinical relapse. The most common grade 3/4 AEs were hematologic. Ibrutinib dose reductions occurred in 41% of patients, most commonly for myelosuppression.

2 arms. Patients had a median age of 58 years, and 40.6% were ages 60 years or older. One-third of patients were female, and 63.3% had an ECOG performance status of 0. Rai stage III/IV disease was noted in 43.1% of patients. Based on fluorescence in situ hybridization, chromosome 11q deletion was observed in 22.2% of patients, trisomy 12 in 18.3%, and chromosome 13q deletion in 33.8%. A $ß_2$ microglobulin level exceeding 3.5 mg/mL was observed in 50.6%, and *IGHV* was unmutated in 71.1%.

After a median follow-up of 33.4 months, the intention-to-treat analysis showed a superior PFS with ibrutinib plus rituximab vs FCR (HR, 0.35; 95% CI, 0.22-0.50; *P*<.0001; Figure 3), with similar results in the eligible study population. Patients with unmutated *IGHV* experienced a prolonged PFS from ibrutinib plus rituximab compared with FCR (HR, 0.26; 95% CI, 0.14-0.50; *P*<.00001; Figure 4), but the difference was not significant in the smaller group of patients with mutated *IGHV* (HR, 0.44; 95% CI, 0.14-1.36; *P*=.07). OS was significantly improved with ibrutinib plus rituximab vs FCR based on intention-to-treat analysis (HR, 0.17; 95% CI, 0.05-0.54; *P*<.0003), again with similar results observed in the eligible study population. Deaths were reported in 4 patients (1.1%) in the ibrutinib/rituximab arm and 10 (5.7%) in the FCR arm. The deaths were attributed to CLL in 1 vs 6, respectively.

Grade 3 to 5 adverse events (AEs) occurred in 72.1% of the FCR arm and 58.5% of the ibrutinib/rituximab arm (*P*=.004). Patients in the FCR arm were more likely to experience neutropenia (*P*<.001), anemia (*P*<.001), thrombocytopenia (*P*<.001), any infection (*P*<.001), neutropenic fever (*P*<.001), atrial fibrillation (*P*=.04), and hypertension (*P*=.01). In the Alliance A041202 trial, patients who received first-line ibrutinib plus rituximab had a median age of 71 years, and these patients experienced a higher rate of grade 3 to 5 AEs than the younger patients in E1912 (7% vs 1%).[7] Compared with patients in the E1912 trial, patients in the Alliance trial were more likely to develop infection (19% vs 5%), atrial fibrillation (6% vs 3%), bleeding (4% vs 1%), and hypertension (34% vs 7%) with ibrutinib plus rituximab.

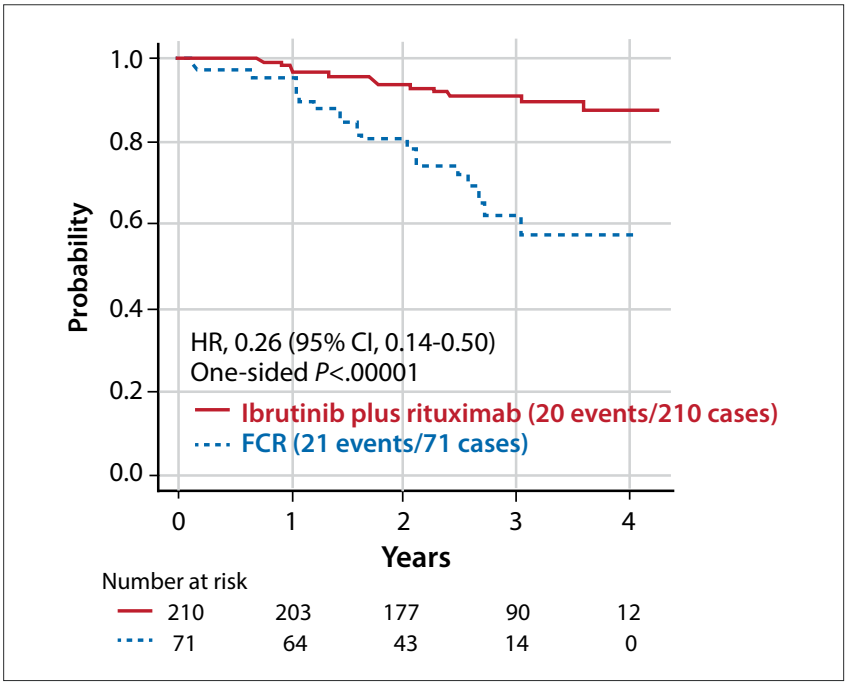

Figure 4. Progression-free survival among patients with unmutated *IGHV* in the E1912 trial of ibrutinib plus rituximab vs FCR in treatment-naive patients. E1912, Ibrutinib and Rituximab Compared With Fludarabine Phosphate, Cyclophosphamide, and Rituximab in Treating Patients With Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio. Adapted from Shanafelt TD et al. ASH abstract LBA-4. *Blood*. 2018;132(suppl 1).[5]

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MURANO Trial Establishes Feasibility of Time-Limited Venetoclax-Rituximab Combination Therapy in Relapsed/Refractory Chronic Lymphocytic Leukemia

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]) compared venetoclax plus rituximab vs bendamustine plus rituximab in patients with relapsed or refractory CLL.[1,2] The trial enrolled 389 patients. All patients received rituximab for 6 months. Patients who were randomly assigned to the venetoclax/rituximab arm also received venetoclax for up to 2 years, and patients in the bendamustine/rituximab arm received bendamustine for 6 months.

After a median of 23.8 months of follow-up, 2-year PFS rates were 84.9% with venetoclax plus rituximab vs 36.3% with bendamustine plus rituximab (HR for progression or death, 0.17; 95% CI, 0.11-0.25; *P*<.001). Venetoclax plus rituximab demonstrated a benefit over bendamustine plus rituximab for all subgroups examined, including patients with the chromosome 17p deletion. After a median follow-up of 36 months, 30 patients in the venetoclax/rituximab arm and 63 in the bendamustine/rituximab arm had discontinued treatment, and venetoclax plus rituximab continued to show a clinically meaningful improvement in OS compared with bendamustine plus rituximab (87.9% vs 79.5%; HR, 0.50; 95% CI, 0.30-0.85). In the bendamustine/rituximab arm, most patients who progressed subsequently received active therapy that included ibrutinib or venetoclax.

At a median follow-up of 9.9 months (range, 1.4-22.5 months) after cessation of venetoclax monotherapy, the estimated 1-year PFS was 87.4% (95% CI, 81.1%-93.8%).[4] MRD is predictive of improved outcomes, including PFS and OS, in CLL patients who receive treatment with chemoimmunotherapy, and MRD negativity

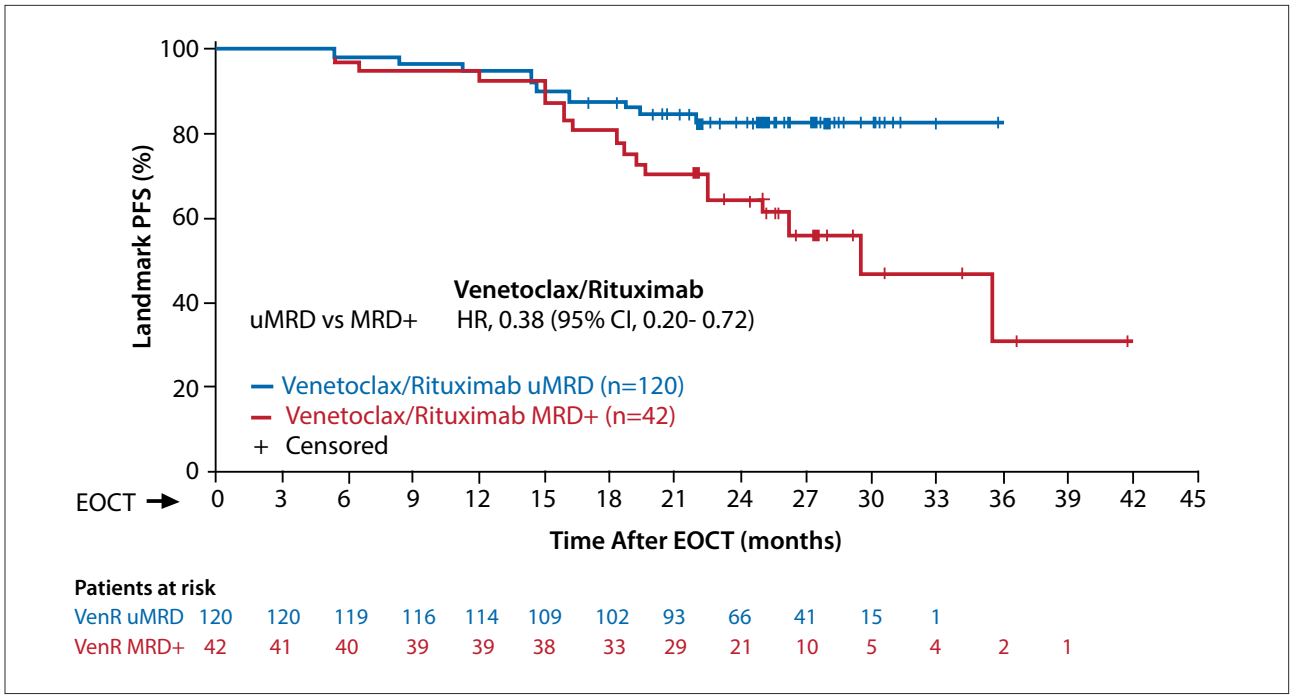

Figure 5. Progression-free survival according to MRD status at the end of treatment with venetoclax plus rituximab among relapsed/refractory patients in the phase 3 MURANO trial. EOCT, end of combination treatment; HR, hazard ratio; MRD, minimal residual disease; MURANO, A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL); uMRD, undetectable MRD. Adapted from Kater AP et al. ASH abstract 695. *Blood*. 2018;132(suppl 1).[4]

is a more robust endpoint than CR.[3] MRD status at the end of 24 months of venetoclax plus rituximab was available for 130 patients. Among these patients, at a median of 9.9 months of posttreatment follow-up, the median PFS was 97.6% in those with undetectable MRD, 87.0% in those with low MRD, and 21.4% in those with high MRD. MRD status was found to be a predictor of disease progression by univariate analysis (P<.0001).

Dr Arnon Kater presented an analysis of MRD.[4] After completion of 6 months of combination therapy, 63% of patients in the venetoclax/rituximab arm vs 15% in the bendamustine/rituximab arm had undetectable MRD.[5] At 24 months, undetectable MRD was again observed in 48% of the venetoclax/rituximab arm vs 2% of the bendamustine/rituximab arm. Consistently high rates of undetectable MRD were observed in the venetoclax/rituximab arm across all subgroups. Patients with undetectable MRD at the end of combination treatment in the venetoclax/rituximab arm had a prolonged PFS (HR, 0.38; 95% CI, 0.20-0.72; Figure 5), as did patients in the bendamustine/rituximab arm (HR, 0.27; 95% CI, 0.14-0.52).[4] Similarly, in both arms, PFS was prolonged in patients with a low MRD status. MRD status was a stronger predictor of PFS than clinical response. In patients with undetectable MRD after treatment, rates of progressive disease and emergence of MRD-positivity were low. The findings represent the first data to demonstrate undetectable MRD as a predictive marker of improved outcome for a fixed-duration, chemotherapy-free treatment regimen.

In the venetoclax/rituximab arm, most grade 3/4 AEs occurred during the 6 months when patients were receiving both drugs. The most common grade 3/4 AE with venetoclax plus rituximab was neutropenia (58.8%), followed by anemia (10.8%). Grade 3/4 tumor lysis syndrome occurred in 3.1% of patients in the venetoclax/rituximab arm.

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Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma: Results From Phase 3 iLLUMINATE

The open-label, multicenter 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) evaluated obinutuzumab in combination with chlorambucil or ibrutinib as first-line treatment in patients with CLL.[1,2] This study enrolled patients ages 65 years or older regardless of comorbidities, as well as patients younger than 65 years with at least 1 coexisting condition, such as a CIRS score higher than 6, a creatinine clearance of less than 70 mL/min, and the *TP53* mutation/chromosome 17p deletion. Patients were randomly assigned to receive chlorambucil (0.5 mg/kg on days 1 and 15) for 6 cycles of 28 days or ibrutinib (420 mg daily) until disease progression or unacceptable toxicity. Patients in both arms also received obinutuzumab (1000 mg, split on days 1-2, plus 1000 mg on days 8 and 15 during cycle 1; then 1000 mg on day 1 for subsequent cycles). The primary endpoint was PFS as assessed by independent review.

The trial enrolled 113 patients in the ibrutinib/obinutuzumab arm and 116 in the chlorambucil/obinutuzumab arm. The median follow-up was 31.3 months (range, 0.2-36.9 months). According to independent assessment, PFS was not reached with ibrutinib plus obinutuzumab vs 19.0 months with chlorambucil plus obinutuzumab (HR, 0.231; 95% CI, 0.145-0.367; *P*<.0001; Figure 6). The estimated 30-month PFS was 79% with ibrutinib plus obinutuzumab vs 31% with chlorambucil plus obinutuzumab. After excluding patients with the chromosome 17p deletion, the ibrutinib combination was associated with a 74% reduction in the risk of progression or death. The ibrutinib combination also showed a consistent benefit over chlorambucil/obinutuzumab in patients with an unmutated *IGHV*, the chromosome 11q deletion, the chromosome 17p deletion, and/or the *TP53* mutation.

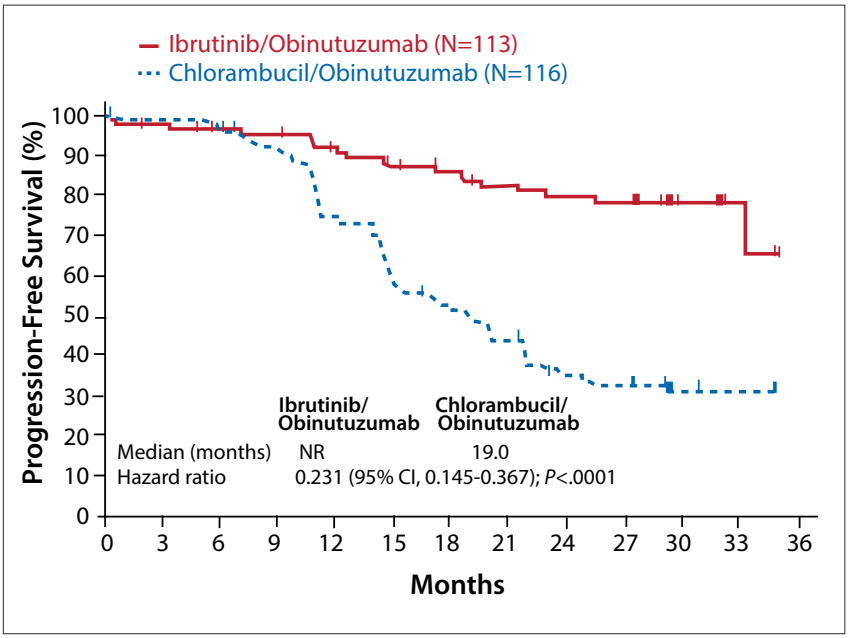

Figure 6. Progression-free survival according to independent assessment in the phase 3 iLLUMINATE trial of ibrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab as frontline therapy. iLLUMINATE, A Multi-Center Study of Ibrutinib in Combination With Obinutuzumab Versus Chlorambucil in Combination With Obinutuzumab in Patients With Treatment Naïve CLL or SLL. NR, not reached. Adapted from Moreno C et al. ASH abstract 691. *Blood*. 2018;132(suppl 1).[1]

For the subpopulation of patients with high-risk disease, which included those with an unmutated *IGHV*, the chromosome 11q deletion, the chromosome 17p deletion, and/or the *TP53* mutation, ibrutinib plus obinutuzumab reduced the risk of disease progression or death by 85%. According to independent review, the ORR was 88% with ibrutinib plus obinutuzumab vs 73% with chlorambucil plus obinutuzumab. The rates of CR/CR with incomplete bone marrow recovery (CRi), were 19% vs 8%, respectively. In the high-risk subpopulation, the ORR was 90% with ibrutinib plus obinutuzumab vs 68% with chlorambucil plus obinutuzumab, with CR/CRi rates of 14% vs 4%, respectively. Rates of undetectable MRD in the bone marrow and/or peripheral blood were 35% with ibrutinib plus obinutuzumab vs 25% with chlorambucil plus obinutuzumab. OS was similar for both arms. However, 40% of patients in the chlorambucil arm crossed over to receive single-agent ibrutinib.

Grade 3/4 AEs were observed in 77% of patients in the ibrutinib/obinutuzumab arm vs 72% in the chlorambucil/obinutuzumab arm. The most common events were neutropenia (36% vs 46%) and thrombocytopenia (19% vs 10%).

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Comparison of Efficacy and Toxicity of CD19-Specific Chimeric Antigen Receptor T Cells Alone or in Combination With Ibrutinib for Relapsed and/or Refractory CLL

The safety and feasibility of therapy with CD-19–directed chimeric antigen receptor (CAR) T cells were evaluated among CLL patients who had previously received ibrutinib.[1] Ibrutinib therapy was discontinued prior to study enrollment. CAR T-cell therapy was administered at 3 doses: 2×10^5 cells/kg, 2×10^6 cells/kg, and 2×10^7 cells/kg. Four weeks after the CAR T-cell infusion, the ORR was 71% (17/24). Twenty patients (83%) developed cytokine release syndrome and 8 (33%) developed neurotoxicity (which led to death in 1 patient). Among 19 patients who received the CAR T-cell infusion and were restaged, the ORR at 4 weeks was 74% and included 4 CRs. Among 12 patients who underwent deep sequencing of the IGH locus, 7 (58%) had no evidence of malignant IGH in the bone marrow.

At the 60th ASH Meeting, Dr Jordan Gauthier provided results of a retrospective study evaluating the outcomes in this cohort of patients in comparison with a cohort of CLL patients who received CD19-directed CAR T-cell therapy plus concurrent ibrutinib.[2] Patients in the concurrent-ibrutinib cohort received ibrutinib at 420 mg daily from at least 2 weeks prior to leukapheresis until at least 3 months after the CAR T-cell infusion. Dose reductions were permitted. The no-ibrutinib cohort included 24 patients and the concurrent-ibrutinib cohort included 19 patients. In the concurrent-ibrutinib cohort, 13 patients (68%) received ibrutinib as planned. One patient died from presumed cardiac arrhythmia after 4 days of ibrutinib therapy.

Among evaluable patients, the ORR was 83% with concurrent ibrutinib vs 65% with no ibrutinib (*P*=.38). Based on bone marrow analysis by flow cytometry, the CR rate was 72% with concurrent ibrutinib vs 74% with no ibrutinib, a difference that was not significant. However, based on sequencing of the *IGH* region, the bone marrow CR rate was 85% (11/13) in the concurrent-ibrutinib cohort vs 50% (7/14) in the no-ibrutinib cohort (*P*=.10). Cross-sectional tumor area (based on the sum of the product of the diameter of up to 6 dominant lesions) was associated with a higher probability of a bone marrow CR by flow cytometry, and successful CAR T-cell expansion was a strong predictor of response according to iwCLL criteria and assessment of nodes and bone marrow (Figure 7).

Cytokine release syndrome of any grade occurred in 74% of patients in the concurrent-ibrutinib cohort vs 92% in the no-ibrutinib cohort

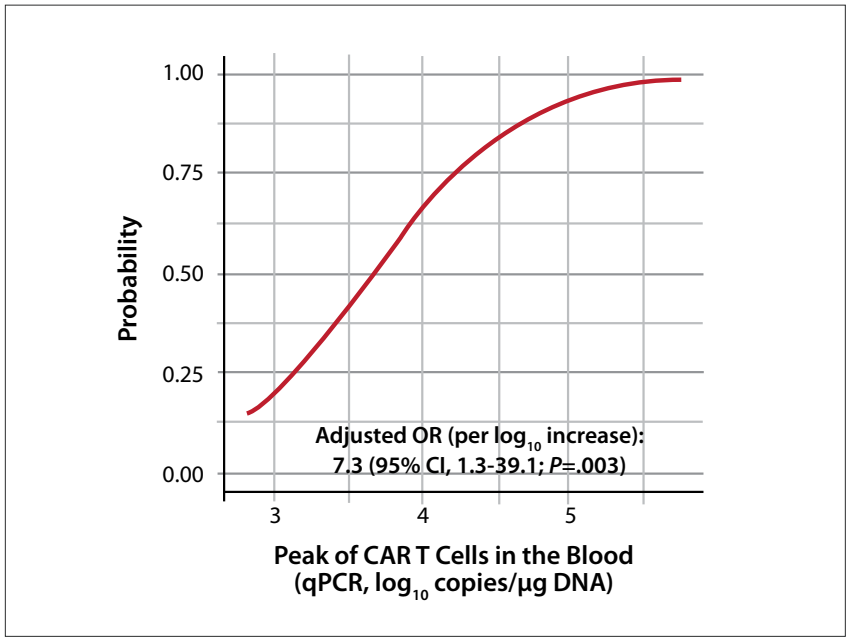

Figure 7. CAR T-cell expansion predicted global response according to iwCLL 2018 criteria in a study of CD19-specific chimeric antigen receptor T cells alone or in combination with ibrutinib in relapsed/refractory patients. CAR, chimeric antigen receptor; iwCLL, the International Workshop on Chronic Lymphocytic Leukemia; OR, odds ratio; qPCR, quantitative polymerase chain reaction. Adapted from Gauthier J et al. ASH abstract 299. *Blood*. 2018;132(suppl 1).[2]

(*P*=.21). However, cytokine release syndrome of grade 3 or higher was less common with concurrent ibrutinib (0% vs 25%; *P*=.03). Grade 3 or higher neurotoxicity was observed in 26% vs 29%, respectively.

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A Phase II Trial of Nivolumab Combined With Ibrutinib for Patients With Richter Transformation

A phase 2 study evaluated nivolumab plus ibrutinib in patients with Richter transformation.[1] Patients received nivolumab (3 mg/kg every 3 weeks) for all treatment cycles, and concomitant ibrutinib (420 mg daily) was administered starting with cycle 2. Eligible patients had Richter transformation characterized by a diagnosis of diffuse large B-cell lymphoma, and an ECOG performance status of 0 to 2. The 24 enrolled patients had a median age of 64.5 years (range, 47-88 years), and 58% were male. Forty-two percent of patients had received prior treatment for Richter transformation, and 83% had received prior treatment for CLL. Based on fluorescence in situ hybridization data from 20 patients, chromosomal abnormalities included the chromosome 17p deletion (45%), the chromosome 11q deletion (20%), and trisomy 12 (20%). Genetic testing identified an unmutated *IGHV* in 72% (13/18), the complex karyotype in 63% (12/19), the *TP53* mutation in 47% (8/17), and the *NOTCH1* mutation in 24% (4/17).

A response was observed in 42% of patients (10/24), including 8 patients with a complete metabolic response and 2 with a partial response. Four additional patients underwent subsequent salvage therapy followed by allogeneic stem cell transplant. Among 13 patients with prior exposure to a BTK inhibitor, the median number of prior therapies was 4, and 3 of these patients (23%) had a response. Among 11 patients with no prior exposure to a BTK inhibitor, the median number of prior therapies was 1, and the response rate was 64% (7/11).

Among 10 patients, the median duration of response was 9.3 months with censoring for allogeneic stem cell transplant and was not reached without censoring for this factor (Figure 8). The median OS was 13.8 months. Among 2 patients who responded to the combination treatment, both had no detectable programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) expression at baseline. Among 3 patients who did not respond, 2 had PD-1 expression on their tumor cells at baseline. The study protocol has been amended to include treatment with ipilimumab, an anti–CTLA-4 antibody.

The combination of nivolumab plus ibrutinib was generally well-tolerated. The most common AEs were grade 1/2 and included skin rash (33%), arthralgia (25%), easy bruising (21%), diarrhea (13%), and atrial fibrillation (4%). Other AEs of interest included grade 4 elevated lipase and amylase in 1, grade 3 pneumonia/pneumonitis or transaminitis in 3, and grade 2 uveitis in 1.

Reference

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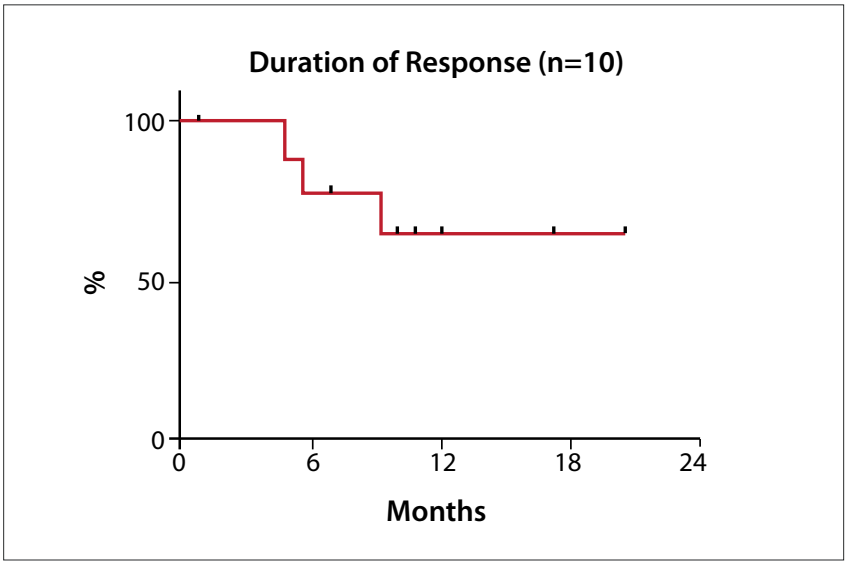

Figure 8. Duration of response without censoring for allogeneic stem cell transplant in a phase 2 study evaluating nivolumab plus ibrutinib in patients with Richter transformation. Adapted from Jain N et al. ASH abstract 296. *Blood.* 2018;132(suppl 1).[1]

Highlights in Chronic Lymphocytic Leukemia From the 60th American Society of Hematology Annual Meeting: Commentary

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Presentations in chronic lymphocytic leukemia (CLL) at the 60th American Society of Hematology (ASH) annual meeting provided important new data. Several studies evaluated the role of ibrutinib in frontline management.

At the plenary session, Dr Jennifer Woyach presented results from the Alliance North American Intergroup Study A041202 (Rituximab and Bendamustine Hydrochloride, Rituximab and Ibrutinib, or Ibrutinib Alone in Treating Older Patients With Previously Untreated Chronic Lymphocytic Leukemia), which compared ibrutinib alone or in combination with rituximab vs bendamustine and rituximab as frontline therapy of CLL in patients older than 65 years.[1] The patients' median age was 71 years. Ibrutinib has a frontline approval that is very broad and not age-restricted.[2] The approval was based on 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), a randomized comparison of ibrutinib vs chlorambucil.[3] Ibrutinib produced significantly longer progression-free survival (PFS). In fact, a recently published 2-year follow-up analysis showed that median PFS was still not reached for ibrutinib vs approximately 15 months for chlorambucil.[4] There was a difference in overall survival in favor of ibrutinib, although it should be mentioned that crossover was allowed in this trial. The RESONATE-2 trial clearly demonstrated that ibrutinib is better than chlorambucil. However, many physicians would treat a patient older than 65 years with a better chemotherapy regimen than chlorambucil. In that setting, the most common regimen is probably bendamustine plus rituximab. The A041202 study therefore compared ibrutinib against this combination, with a primary endpoint of PFS. The trial also evaluated overall survival and whether the addition of rituximab to ibrutinib improves outcomes. Phase 2 data have shown that the addition of rituximab to ibrutinib accelerates the response to ibrutinib.[5] The underlying reason is that in most patients, single-agent ibrutinib causes lymphocytosis, which resolves completely over time.[6] The addition of rituximab abrogates the lymphocytosis.[7] However, it was not known whether the addition of the antibody leads to more deep or durable remissions. A randomized trial from MD Anderson attempted to address this question.[5] The study compared ibrutinib with or without rituximab in patients with CLL; most had relapsed disease. The primary endpoint was 24-month PFS. The trial found that there was no long-term benefit with the addition of rituximab; the Kaplan-Meier curves for PFS overlapped completely. A caveat to this study finding is that with a population of patients who have relapsed disease, it might be expected that most patients would have already received rituximab as part of their frontline chemoimmunotherapy regimen and theoretically might have some degree of resistance to this agent.

The A041202 study evaluated frontline therapy, so resistance was not an issue.[1] This large trial enrolled more than 500 patients. The population was older, with a median age of approximately 71 years. PFS, the primary endpoint, was dramatically different in the ibrutinib arms vs the bendamustine/rituximab arm. At the 24-month estimate, the PFS was 74% with bendamustine/rituximab, 87% with ibrutinib monotherapy, and 88% with ibrutinib/rituximab. Therefore, the trial showed no difference in outcomes with the addition of rituximab to ibrutinib, but both of these regimens were significantly better than bendamustine/rituximab. This improvement was particularly evident in 17p-deleted patients. Currently, patients with the 17p deletion are no longer treated with chemotherapy, and they would now be excluded from this type of trial. The superiority of the ibrutinib arms was also evident in patients with a complex karyotype. Benefits were unclear, however, in patients with the mutated immunoglobulin heavy chain variable (*IGHV*) gene, who respond best to chemotherapy. In this group, there was not a large difference among the treatment arms, but there was a trend toward improvement with ibrutinib. Longer follow-up may identify a difference.

The response rates overall were 93% with ibrutinib monotherapy and

94% with ibrutinib/rituximab, compared with 81% with bendamustine/rituximab. The complete response rate, however, was higher with bendamustine/rituximab, at 26%, vs 7% with ibrutinib monotherapy and 12% with ibrutinib/rituximab. So far, the overall survival rates did not differ according to treatment; in this frontline population, the 24-month survival exceeded 90% in all arms. This lack of a difference is not surprising because most patients who progress on bendamustine/rituximab can go on to receive ibrutinib-based therapy as a salvage regimen.

As expected, there was more hematologic toxicity, predominantly neutropenia, with chemotherapy. There was also more febrile neutropenia with the chemotherapy, which again is not surprising. The only toxicity that was significantly higher in the ibrutinib arms was hypertension. This known side effect can usually be addressed with antihypertensive agents.[3]

The real question is whether the results of this trial are practice-changing: will physicians who use bendamustine/rituximab as frontline therapy switch to ibrutinib, without evidence of a survival benefit? Physicians might still reserve ibrutinib for use as a salvage regimen, based on the following rationale. Most patients with CLL cannot be cured. (There may be a cure fraction among patients with the *IGHV* mutation who are treated with fludarabine, cyclophosphamide, and rituximab [FCR].[8]) The goal, therefore, is to sequence treatments—getting a certain number of years from each—to keep patients alive long enough so that they die from other causes. In this study, the median PFS was 41 months with bendamustine/rituximab.[1] Therefore, this regimen provides approximately 3 and a half years until disease progression, and possibly even more time until the next therapy is needed. It may make sense to use chemotherapy as upfront treatment because administration only becomes more problematic as a patient ages. Ibrutinib is a great salvage regimen associated with long remissions. The results of this study could give physicians the confidence to use bendamustine/rituximab as upfront treatment.

A late-breaking abstract from the Eastern Cooperative Oncology Group (ECOG)/American College of Radiology Imaging Network (ACRIN) group provided results from another important large, randomized trial in the frontline setting for CLL.[9] The study compared ibrutinib and rituximab vs FCR in previously untreated patients with CLL. There was no single-agent ibrutinib arm. FCR is the gold standard for these patients. The head-to-head German CLL10 study showed that PFS was approximately 1 year longer with FCR than bendamustine/rituximab.[10] In the United States, however, FCR is used less often than bendamustine/rituximab because FCR is more difficult to administer, a clinical perception that was confirmed by the CLL10 trial. FCR is more likely to cause myelosuppression and grade 3 to 4 infection,[11] so most physicians reserve it for younger, fit patients.

The ECOG-ACRIN trial enrolled patients younger than 70 years who did not have deletion 17p.[9] More than 500 patients were randomly assigned to treatment with ibrutinib/rituximab or standard-dose FCR. The primary endpoint was PFS. The patients' median age was 58 years, which was much younger than that in the Alliance trial[1] and reflects the fact that younger, fit patients are the better candidates for FCR.[11]

As in the Alliance trial, PFS was significantly better with ibrutinib/rituximab vs FCR, although no median PFS was reached for either arm.[9] The study also analyzed results according to the patients' mutational status. Those with the *IGHV* mutation had a trend toward improvement with ibrutinib/rituximab that was not statistically significant. Among patients with an unmutated *IGHV*, ibrutinib/rituximab significantly improved PFS.

The trial did not resolve whether ibrutinib will recreate the plateau that exists for FCR, partly because the follow-up duration was short. A plateau was also not seen among patients with the *IGHV* mutation treated with FCR, again because it is too early.

A surprising finding was a survival advantage with ibrutinib/rituximab.[9] There were 4 deaths in the ibrutinib/rituximab arm vs 10 in the FCR arm. The data were reported early, however, and the low number of deaths overall may have skewed the *P* value. With longer follow-up, the outcome may become more similar. FCR is known to be associated with grade 3 to 4 infections,[11] but infections were not the primary cause of death in the FCR arm. In the FCR arm, 6 of the deaths were caused by progressive CLL. This finding raises the question of why the patients developed progressive disease so early. One possible explanation is that the trial excluded patients with the 17p deletion, but it did not screen for the *TP53* mutation. It is possible that the trial enrolled patients with the *TP53* mutation, who respond poorly to chemotherapy. The presentation at ASH did not specify why the patients with progressive disease did not cross over to the ibrutinib arm.

In terms of the toxicity, as expected, there was significantly more neutropenia, anemia, thrombocytopenia, and infections with FCR. In the ibrutinib arm, there was more atrial fibrillation, a known side effect, and hypertension.

This interesting trial clearly showed that ibrutinib led to a better PFS than the best chemoimmunotherapy regimen now available. Like the Alliance trial, however, the results may not be practice-changing, for the following reasons. In the United States, most patients treated in the community setting are older than 71 years and would not be candidates for FCR. The one setting where many experts still use FCR is in the *IGHV*-mutated population. In the past 2 years, 3 publications showed a plateau in the PFS curve with FCR among patients with the *IGHV* mutation.[8,12,13] A study from MD Anderson, where the

FCR regimen was developed, had the longest follow-up.[8] At 10 to 16 years, approximately 60% of these patients were free of progression. Many patients also showed no minimal residual disease, which suggests that there may be a cure fraction. It is not yet known whether physicians will change their treatment approach based on the results of this trial. A confounding factor is the survival advantage seen with ibrutinib, which requires further explanation.

The frontline randomized iLLUMINATE study (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.[14] A criticism of the RESONATE-2 trial[3] (which led to the approval of ibrutinib as a single agent when it showed superiority over single-agent chlorambucil) was that the standard of care was chlorambucil/obinutuzumab by the time the results were reported. As with any type of chemotherapy in lymphoid malignancies, there are now strong data from randomized trials, including CLL11, showing that obinutuzumab plus chlorambucil is better than chlorambucil alone.[15] The CLL11 trial had a third arm of chlorambucil and rituximab, and this regimen was clearly inferior to chlorambucil and obinutuzumab (which is approved for the frontline treatment of CLL). In the RESONATE-2 trial, however, the superiority of ibrutinib over chlorambucil was so large that it is hard to imagine it would not have remained so even with the addition of obinutuzumab to chlorambucil. Therefore, a randomized trial was probably not needed to confirm that ibrutinib was better. In the frontline CLL11 trial, chlorambucil and obinutuzumab produced a median PFS of approximately 26 months.[15] This PFS was significantly better than chlorambucil with or without rituximab, but far inferior to that of ibrutinib, which was still not reached after 24 months of follow-up.[4]

An interesting aspect to the iLLUMINATE trial was that it combined obinutuzumab with ibrutinib. Nearly all of the other trials that combined ibrutinib with an antibody used rituximab, and showed no improvement in outcome.[5,7] (In contrast, the addition of antibodies to chemotherapy always improves outcome in lymphoid malignancies.) More than 200 patients were randomly assigned to receive ibrutinib/obinutuzumab or chlorambucil/obinutuzumab.[14] iLLUMINATE is a registration trial. The patients' median age was approximately 71 years, so this trial enrolled an older population, as would be expected. According to an independent review committee, the PFS at 2 and a half years was 79% with ibrutinib/obinutuzumab vs 31% with chlorambucil/obinutuzumab. The median PFS with chlorambucil/obinutuzumab was 19 months as assessed by the independent review committee and 22 months by investigator assessment.

The difference was even more dramatic among high-risk patients: those with unmutated *IGHV,* the deletion 11q, the deletion 17p, or the *TP53* mutation. If this trial were being designed now, it would exclude patients with the 17p deletion or the *TP53* mutation, who do not respond well to any type of chemotherapy.

The overall response rate was higher with ibrutinib/obinutuzumab, at 88%, vs 73% with chlorambucil/obinutuzumab. Interestingly, the complete response rate was higher with ibrutinib/obinutuzumab at 19%, vs 8% with the chemotherapy combination.

The rate of undetectable minimal residual disease, meaning less than 1 CLL cell in 10,000 cells, was higher with ibrutinib/obinutuzumab. Rates of undetectable minimal residual disease (MRD) were approximately 20% in the bone marrow and 30% in the peripheral blood with ibrutinib/obinutuzumab vs 17% and 20%, respectively, with chlorambucil/obinutuzumab. An interesting observation from the ibrutinib/rituximab data was that the complete response rates were low and the rates of undetectable MRD were very low. Essentially, undetectable MRD was not seen. The iLLUMINATE trial suggests that there may be a role for the antibody obinutuzumab in combination with ibrutinib. With the rate of MRD negativity being only 20%, however, this regimen will not impact overall outcomes for most patients. In this trial, the rates of overall survival were higher than 80% for both treatment arms at a median follow-up of 2 and a half years. The similarity is not surprising because many patients who relapse on chlorambucil will go on to receive ibrutinib, and the follow-up duration was short.

Regarding the toxicity profile, there was more myelosuppression and fevers with chemotherapy. Atrial fibrillation was more common with ibrutinib. Rates of hypertension were similar in both arms.

The results of this trial may be practice-changing in Europe, where chlorambucil plus obinutuzumab is the standard of care. This regimen is far less common in the United States.

The phase 2 trial of ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) from MD Anderson enrolled only patients with the *IGHV* mutation; patients with the deletion 17p or the *TP53* mutation were excluded.[16] As I mentioned, FCR appears to provide a plateau on the PFS curve for patients with mutated *IGHV*.[8] The researchers at MD Anderson did not want to give up chemotherapy in this population because of the possibility of a cure fraction. The idea behind the study was to alter the standard chemotherapy regimen to improve outcomes and reduce toxicity. Because obinutuzumab is the better antibody with chlorambucil, the researchers substituted it for rituximab in the standard FCR regimen. An additional consideration was that ibrutinib improves the outcome of chemotherapy. Several years ago, the HELIOS trial (A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small

Lymphocytic Lymphoma; CLL3001) evaluated bendamustine and rituximab with or without ibrutinib, showing that the addition of ibrutinib improved outcomes.[17] Ibrutinib was therefore added to this regimen, but chemotherapy was limited to 3 cycles to minimize the associated short-term and late-term toxicity. Treatment continued with ibrutinib and obinutuzumab.

All patients received obinutuzumab with fludarabine/cyclophosphamide for 3 cycles, plus ibrutinib at the standard dose of 420 mg/day. After 3 cycles, all patients were treated with at least 9 more months of ibrutinib, for a total treatment duration of 1 year. After the 3 cycles, patients then received obinutuzumab for 3 more courses if they had a complete response and were MRD-negative after the 3 months of chemotherapy. Patients with only a partial response or who were MRD-positive received obinutuzumab for 9 more courses. After 12 cycles, patients with undetectable MRD would stop ibrutinib, so all therapy would be discontinued. Patients who were MRD-positive would continue to receive ibrutinib.

The trial enrolled 45 patients, and response was evaluable in 44. The median follow-up was nearly 2 years. The patients' median age was 60 years. This young age is not surprising, as this group of patients can reasonably tolerate FCR, and by extension, the regimen evaluated in the trial.

After 3 cycles of ibrutinib plus chemotherapy, the rate of MRD undetectability was high, at 89%. This rate appeared to improve with time. Among the 32 patients who reached 1 year of follow-up, all had undetectable MRD and were able to stop treatment. These data compare well with that of historical controls. In the CLL10 trial of FCR vs bendamustine/rituximab, MRD was undetectable in 62% of patients with the *IGHV* mutation after 6 cycles of therapy.[10]

The trial of iFCG also analyzed serial bone marrow MRD with a very sensitive, next-generation sequencing assay called clonoSEQ. This assay can detect 1 CLL cell in 10^5 or 10^6 cells. Interestingly, of the 18 patients with sequencing data available at 12 months, all patients were MRD-negative by the standard assay, and 71% were MRD-negative according to the clonoSEQ assay, suggesting that these remissions were very deep. The median follow-up after stopping ibrutinib was a little more than a year, and no patient had developed progressive disease.

These interesting data suggest that it is possible to administer very limited chemotherapy in combination with ibrutinib to this group of patients with mutated *IGHV*. This regimen has the potential to produce very high rates of MRD negativity. Importantly, it may allow therapy to be discontinued, which is attractive to patients as well as payers. It will be interesting to learn the long-term outcome among patients who stop therapy at 1 year.

Disclosure

Dr O'Brien is a consultant for Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc, Vaniam Group LLC, AbbVie, and Alexion. She has received research support from Kite, Regeneron, and Acerta. She is a consultant and/or has received research support from Gilead, Pharmacyclics, TG Therapeutics, Pfizer, and Sunesis.

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