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A SPECIAL MEETING REVIEW EDITION

Highlights in Chronic Lymphocytic Leukemia From the 2016 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2016 American Society of Hematology Annual Meeting and Exposition
December 3-6, 2016 • San Diego, California

Special Reporting on:

- Five-Year Experience With Single-Agent Ibrutinib in Patients With Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia
- Twice Daily Dosing With the Highly Specific BTK Inhibitor, BGB-3111, Achieves Complete and Continuous BTK Occupancy in Lymph Nodes, and Is Associated With Durable Responses in Patients (pts) With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
- Integrated and Long-Term Safety Analysis of Ibrutinib in Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
- Acalabrutinib Monotherapy in Patients With Ibrutinib Intolerance: Results From the Phase 1/2 ACE-CL-001 Clinical Study
- Updated Efficacy and Safety From the Phase 3 RESONATE-2 Study: Ibrutinib as First-Line Treatment Option in Patients 65 Years and Older With Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia
- Updated Analysis of Overall Survival in Randomized Phase III Study of Idelalisib in Combination With Bendamustine and Rituximab in Patients With Relapsed/Refractory CLL
- CLL2-BIG – A Novel Treatment Regimen of Bendamustine Followed By GA101 and Ibrutinib Followed by Ibrutinib and GA101 Maintenance in Patients With Chronic Lymphocytic Leukemia (CLL): Results of a Phase II-Trial

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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#1 PRESCRIBED ORAL CLL THERAPY.*
MORE THAN 20,000 PATIENTS TREATED SINCE APPROVAL[1†]

MAKE IMBRUVICA® YOUR FIRST STEP

Approved in frontline CLL with or without 17p deletion[2]

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for:

- 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 up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half 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 postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 9%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 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 antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 5% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4% to 13%).

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

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this

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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 not included in the RESONATE™-2 trial[3]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

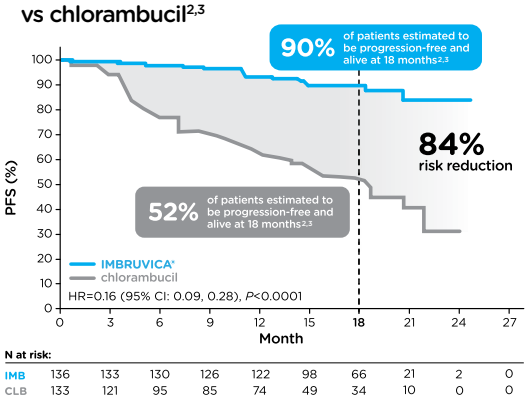
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil[2,3]



PRIMARY ENDPOINT: PFS

- Median follow-up was 18 months[3]
- IMBRUVICA® median PFS not reached[2]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[2]
- PFS was assessed by an IRC per revised IWCLL criteria[3]

Adverse reactions ≥20% across CLL/SLL registration studies[2]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

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.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia‡ (64%), thrombocytopenia‡ (63%), diarrhea (43%), anemia‡ (41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia (21%).

‡Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL/SLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL/SLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

*Based on market share 2016 July YTD data from IMS.
†Based on IMS data February 2014 to date.

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 leukemia.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2016. **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) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of 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 of clinical benefit in confirmatory trials *[see Clinical Studies (14.1) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

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 up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half 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 have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed 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 (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 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 (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

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 embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. 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]*
- Atrial Fibrillation *[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 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
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* Decrease of Hemoglobin, Platelets, or Neutrophils 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 and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 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 1, 2, 3 and 4 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 1, 2, 3 and 4 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 1: 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 1

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
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.

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Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

	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.

Study 2: 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 Study 2 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 in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
Body System Adverse Reaction	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
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 system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

	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

* Based on laboratory measurements per IWCLL criteria.

Study 3: 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 Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

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
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 system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Study 4: 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 Study 4 in patients with previously treated CLL/SLL.

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Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

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
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 system organ class 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: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

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 the WM trial.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).

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 (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[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. 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 malformations *[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.

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.

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 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.

Geriatric Use: Of the 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA *[see Clinical Studies (14.2) in Full Prescribing Information]*.

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Table of Contents

Five-Year Experience With Single-Agent Ibrutinib in Patients With Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

As a key cytoplasmic component of the B-cell receptor pathway, Bruton tyrosine kinase (BTK) plays a critical role in controlling proliferation, survival, and differentiation of B-lineage lymphoid cells.[1] Ibrutinib is an orally available small molecule that selectively binds to the cysteine 481 residue in the ATP binding domain of BTK, halting kinase activity and inhibiting signaling downstream from the B-cell receptor. Ibrutinib is approved by the US Food and Drug Administration (FDA) as a once-daily treatment for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who are treatment-naive or who have relapsed/refractory disease.[2] Results from the phase 1b/2 study PCYC-1102 and the extension study PCYC-1103 demonstrated the efficacy and safety of ibrutinib monotherapy in patients with CLL/SLL, with a manageable safety profile that allows patients to continue on treatment for an extended duration.[3-6] Three-year follow-up data yielded an objective response rate (ORR) of 90% and a complete response (CR) rate of 7% in the overall study population while demonstrating durable remissions and improved quality of response over time.

Dr Susan O'Brien presented 5-year follow-up results from the PCYC-1102 and PCYC-1103 trials, including efficacy and safety outcomes in the overall population and in patients with risk factors.[7] PCYC-1102 enrolled 31 treatment-naive CLL/SLL patients ages 65 years or older and 101 patients with relapsed or refractory CLL/SLL. The latter group included 24 patients with high-risk disease, defined as disease progression within 24 months of initiating chemoimmunotherapy. In the treatment-naive vs relapsed/refractory cohorts, the median age was 71 vs 64 years, Rai stage III/IV disease was present in 55% vs 57% of patients, and 19% vs 54% had bulky disease, respectively. Cytogenetic abnormalities observed in the 2 cohorts included del(17p) (6% vs 34%), del(11q) (3% vs 35%), trisomy 12 (26% vs 12%), del(13q) (55% vs 47%), and complex karyotype (13% vs 37%). The immunoglobulin heavy chain variable (*IgHV*) region was unmutated in 48% of the treatment-naive patients vs 78% of the relapsed/refractory patients. In the relapsed/refractory cohort, patients had a median of 4 lines of prior therapy (range, 1-12).

The ORR in the entire study population of 132 patients was 89%, including 14% CRs, 71% partial responses (PRs), and 3% PRs with lymphocytosis. ORR was 87% in the treatment-naive patients vs 89% in the relapsed/refractory patients, including CRs of 29% vs 10%. Among the patients with relapsed/refractory disease, the ORR was 97% in patients with del(11q), 90% in patients with unmutated *IgHV*, 90% in those with complex karyotype, and 79% in those with del(17p), including CR rates of 9%, 9%, 7%, and 6%, respectively.

ABSTRACT SUMMARY Acalabrutinib Monotherapy in Patients With Richter Transformation From the Phase 1/2 ACE-CL-001 Clinical Study

Approximately 5% to 10% of CLL patients develop Richter transformation, in which CLL transforms into an aggressive lymphoma. Patients with Richter transformation have a median PFS of approximately 6 months and median OS of less than 1 year. The ongoing phase 1/2 ACE-CL-001 trial is investigating the safety and efficacy of acalabrutinib, with preliminary results available in a cohort of patients with Richter transformation (Abstract 60). Twenty-nine patients with Richter transformation received acalabrutinib (200 mg) twice daily. Patients had a median age of 66 years (range, 43-82), 14% had B symptoms, 7% had bulky disease of at least 10 cm, the median number of prior therapies was 4 (range, 0-13), and nearly half had received prior ibrutinib. AEs of grade 3 or greater observed in at least 2 patients included anemia and neutropenia (14% each), hypercalcemia and back pain (10% each), fatigue, asthenia, and acute kidney injury (7% each). Serious AEs occurred in 55% of patients, but no patients discontinued owing to an AE. The median time on treatment was 3.4 months (range, 1.7-12.0 months). The ORR was 38.1%, including 9.5% CRs and 28.6% PRs. The median duration of response was 5.2 months (range, 0.3 to 6.5+ months). Median PFS was 2.1 months (range, 0.03+ to 8.3+ months). Among the 8 responding patients, 3 remained on study. Two responders received a stem cell transplant.

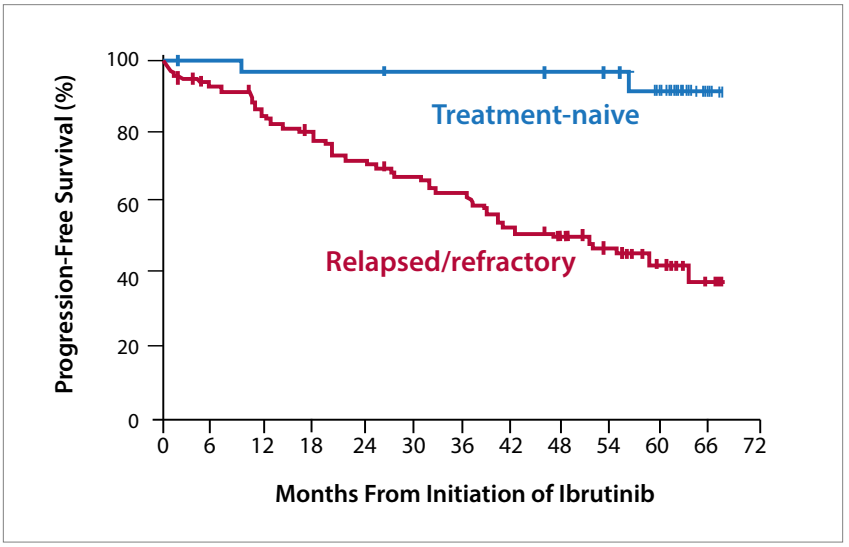

Figure 1. Five-year progression-free survival with single-agent ibrutinib. Adapted from O'Brien SM et al. ASH abstract 233. *Blood.* 2016;128(suppl 22).[7]

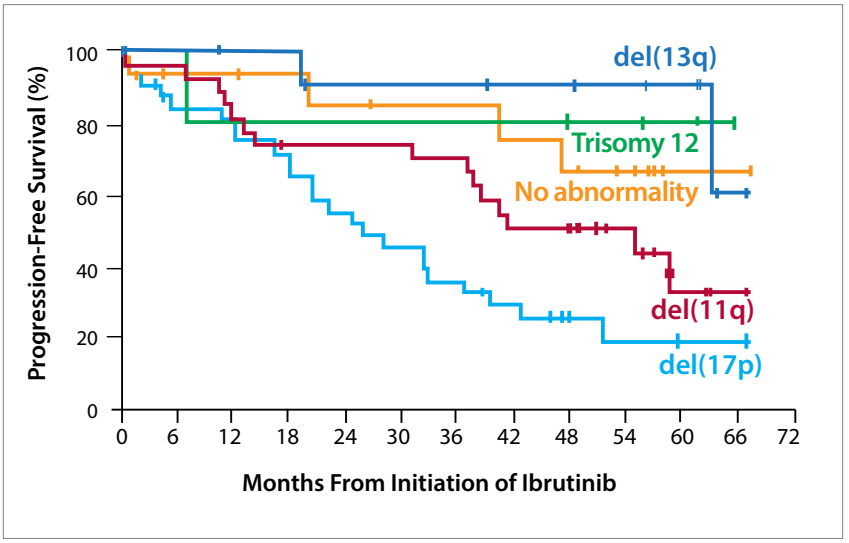

Figure 2. Five-year progression-free survival with single-agent ibrutinib according to mutational status. Adapted from O'Brien SM et al. ASH abstract 233. *Blood.* 2016;128(suppl 22).[7]

At 5 years, the progression-free survival (PFS) rates were 92% in the treatment-naive cohort vs 43% in the relapsed/refractory cohort (Figure 1). Five-year overall survival (OS) rates were 92% vs 57%, respectively. Among the patients with relapsed or refractory disease, patients with mutated *IgHV* vs unmutated *IgHV* demonstrated 5-year PFS rates of 53% vs 38% and 5-year OS rates of 66% vs 55%, respectively. However, the Kaplan-Meier curves for both outcomes showed considerable overlap. In the 34 patients with del(17p) at baseline, median PFS was 26 months (Figure 2), and median OS was 57 months. Five-year PFS was 19%, and 5-year OS was 32%. In the 28 patients with del(11q) at baseline, median PFS was 55 months, and median OS was not reached. Five-year PFS was 33%, and 5-year OS was 61%.

Among patients with a complex karyotype, 90% had relapsed or refractory disease. These patients had received a median of 4 prior therapies. PFS and OS were reduced in this group of patients. For patients without the complex karyotype, 5-year PFS was 69% and OS was 84%, vs 36% and 46% in patients with a complex karyotype. Five-year survival decreased with the number of prior therapies. Five-year PFS was 92% in treatment-naive patients vs 38% in those treated with 4 or more prior therapies. Five-year OS was 92% vs 47%, respectively. Multivariate analysis revealed del(17p) as the only significant predictor of PFS and OS.

Ibrutinib therapy was generally well-tolerated. The rate of adverse events (AEs) of grade 3 or higher decreased over time. In the entire study population, onset of treatment-emergent AEs of grade 3 or greater was highest in the first year of treatment and decreased during subsequent years. The most common AEs of grade 3 or higher were hypertension (26%), pneumonia (22%), neutropenia (17%), and atrial fibrillation (9%). The most common nonhematologic AEs were pneumonia and hypertension in previously treated patients vs hypertension and diarrhea in treatment-naive patients.

For the treatment-naive patients vs those with relapsed/refractory disease, the median time on study was 62 months (range, 1-67 months) vs 49 months (range, 1-67 months). In the 2 cohorts, 65% vs 30% of patients remained on therapy, respectively. Discontinuation of study treatment occurred in 20% of patients owing to an AE and in 26% of patients owing to disease progression. The predominant reasons for discontinuing therapy differed in the 2 patient groups, with progressive disease accounting for 3% in the treatment-naive cohort vs 33% in the relapsed/refractory cohort. AEs

accounted for 19% vs 21% of discontinuations, respectively.

References

1. Jeyakumar D, O'Brien S. The next generation of targeted molecules for the treatment of chronic lymphocytic leukemia. *Oncology* (*Williston Park*). 2016;30(11):219811.
2. Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics, Inc; 2016.
3. Smith DD, Goldstein L, Cheng M, et al. Modeling absolute lymphocyte counts after treatment of chronic lymphocytic leukemia with ibrutinib. *Ann Hematol*. 2015;94(2):249-256.
4. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood*. 2015;125(16):2497-2506.
5. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
6. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014;15(1):48-58.
7. O'Brien SM, Furman RR, Coutre SE, et al. Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia [ASH abstract 233]. *Blood*. 2016;128(suppl 22).

ABSTRACT SUMMARY The Development and Expansion of Resistant Subclones Precedes Relapse During Ibrutinib Therapy in Patients With CLL

A study was conducted in CLL patients treated with ibrutinib to identify risk factors for relapse and prevalence of known resistance mutations, and to develop a monitoring strategy to identify patients at high risk of relapse (Abstract 55). The study included 308 patients from 4 clinical trials at a single cancer center. Patients had a median age of 65 years (range, 26-91 years), two-thirds had Rai stage III/IV disease, and the median number of prior therapies was 3 (range, 0-16). At a median follow-up of 40.5 months (range, 4-71 months), 136 remained on study, 14 received a transplant or therapy at another institution, and 158 had discontinued. Eighty-three patients experienced disease progression, including 28 with disease transformation and 55 with progressive CLL. Baseline risk factors for ibrutinib discontinuation owing to transformation included complex karyotype ($P<.01$) and MYC abnormalities ($P=.051$). Factors associated with discontinuation owing to CLL progression included age younger than 65 years, presence of del(17p), and complex karyotype ($P<.05$ for each). Deep sequencing of DNA from 46 patients with relapsed CLL revealed the presence of mutations in *BTK* or *PLCG2* in 84.8% of patients (95% CI, 71.1%-93.7%). Serial samples from 15 patients demonstrated that a clone of resistant cells was first detected at a median of 9.3 months prior to clinical relapse (95% CI, 7.2-11.7 months). Subsequent analyses have identified clonal expansion of cells, with the *BTK* C481S mutation as a key component of relapse. Subsequent treatment with venetoclax showed a rapid decrease in C481S allele frequency.

Twice Daily Dosing With the Highly Specific BTK Inhibitor, BGB-3111, Achieves Complete and Continuous BTK Occupancy in Lymph Nodes, and Is Associated With Durable Responses in Patients (pts) With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

BTK is critical for cellular survival and for clonal expansion of malignant cells in CLL/SLL.[1] BGB-3111 is an irreversible, highly selective, second-generation inhibitor of BTK, with high oral bioavailability and exposure levels.[2] In vitro studies have demonstrated comparable binding potency against BTK for ibrutinib and BGB-3111, with IC_{50} values of 0.34 nM and 0.36 nM, respectively, in the Rec-1 proliferation assay. Moreover, BGB-3111 has greatly improved binding selectivity compared with ibrutinib, showing reduced binding to the epidermal growth factor receptor, interleukin-2–inducible T-cell kinase, Janus kinase 3 (JAK3), HER2/ERBB2, and TEC kinase. The improved binding selectivity is anticipated to correlate with reductions in certain AEs, including diarrhea, bleeding, and atrial fibrillation.

Dr Constantine Tam presented results from the first-in-human clinical trial of BGB-3111.[3] The phase 1 trial included a dose-escalation component followed by expansion. Patients with relapsed or refractory B-cell malignancies according to World Health Organization criteria were enrolled into cohorts for treatment with BGB-3111 dosed once daily at 40 mg, 80 mg,

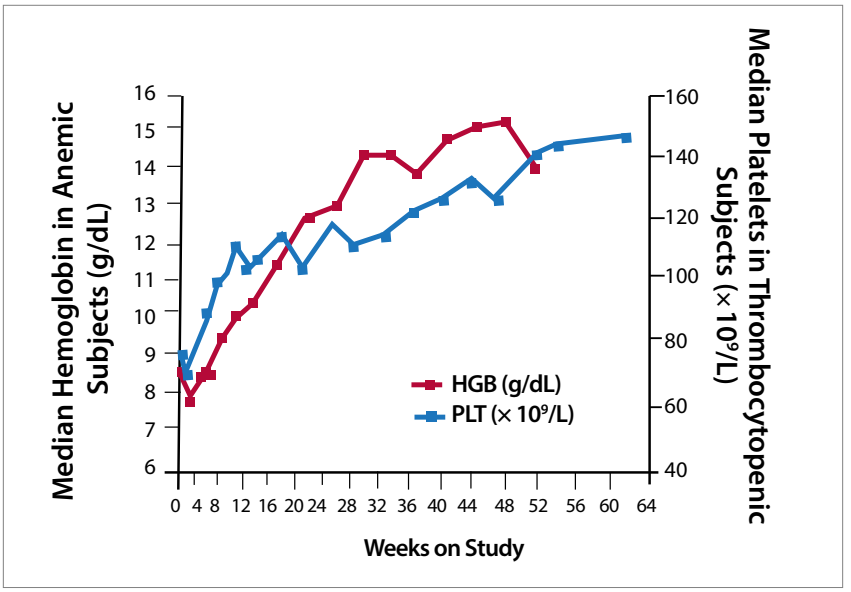

Figure 3. Median hemoglobin levels in patients with anemia treated with the BTK inhibitor BGB-3111. BTK, Bruton tyrosine kinase; PLT, platelet; HGB, hemoglobin. Adapted from Tam CS et al. ASH abstract 642. *Blood*. 2016;128(suppl 22).[3]

160 mg, or 320 mg or dosed twice daily at 160 mg, using a modified 3+3 dose escalation design and disease-specific expansion cohorts. Patients with relapsed or refractory B-cell malignancies were assigned to BGB-3111 at 160 mg twice daily or 320 mg once daily for pharmacodynamic assessments. In order to assess BTK occupancy in the lymph nodes at the time of trough drug exposure, paired lymph node biopsies were taken from these patients at baseline and prior to dosing on day 3. BGB-3111 exposure increased in a dose-dependent manner from 40 mg to 320 mg daily. The maximum concentration and area under the curve of BGB-3111 in patients treated with 80 mg daily were similar to those observed in patients treated with ibrutinib dosed at 560 mg daily.[4] Free drug exposure from BGB-3111 (40 mg daily) was similar to that observed from ibrutinib (560 mg daily). In cohorts receiving the 2 highest doses of BGB-3111, drug exposure levels were approximately 8-fold higher compared with ibrutinib (560 mg daily). Complete BTK occupancy was observed in peripheral blood mononuclear cells in the lowest dose cohort. Twenty patients with relapsed or refractory B-cell malignancies were enrolled in the pharmacodynamic assessment cohorts. The median trough BTK occupancy in the lymph nodes was 100% in patients receiving BGB-3111 at 160 mg twice daily vs 94% in those receiving 320 mg once daily (P=.002), and the proportion of patients with greater than 90% trough occupancy at all time points was 94% vs 58%, respectively.

Among the 63 enrolled patients with CLL/SLL, 17 had less than 12 weeks of follow-up and were therefore not included in the analysis. One patient discontinued treatment owing to an AE. Sixty-two patients remained on the study with no evidence of progressive disease. The 46 patients had a median age of 67 years (range, 24-79 years), and the median follow-up was 8.6 months (range, 2.2-20.9 months). Nine patients were treatment-naive. The 37 patients with relapsed or refractory disease had received a median of 2 prior therapies (range, 1-6). Molecular risk factors included del(17p)/*TP53* mutation (18%), del(11q) (35%), and unmutated *IgHV* (75%).

The ORR was 96%, including 67% PRs and 28% PRs with lymphocytosis. In the 17 patients with del(17p) and/or del(11q), the ORR was 100%. The overall study group showed a dramatic reduction in lymph node burden by the first scan, which was administered 3 months after treatment was initiated. The median absolute lymph node count peaked at approximately 8 weeks after initiating treatment and returned to baseline after approximately 3 to 4 months. In anemic patients, median hemoglobin levels increased over time, from approximately 9 g/dL at baseline to approximately 15 g/dL by week 60 (Figure 3). Similarly, in patients with a platelet count of less than 100,000/μL at baseline, the median platelet count improved over time.

The most common AE of any grade was bleeding (48%), followed by upper respiratory tract infection (33%) and fatigue (28%). Sixteen patients (35%) had at least 1 AE of grade 3 or greater, 10 patients (22%) had at least 1 serious AE, and 1 patient (2%) discontinued treatment owing to an AE. Diarrhea, bleeding, and atrial fibrillation are known AEs associated with ibrutinib therapy. In the current analysis of 46 patients, 9 patients (20%) experienced diarrhea; all episodes were grade 1 or 2 in severity. One patient (2%) experienced grade 3/4 hemorrhage and 1 patient (2%) experienced atrial fibrillation.

References

1. ten Hacken E, Burger JA. Molecular pathways: targeting the microenvironment in chronic lymphocytic leukemia–focus on the B-cell receptor. *Clin Cancer Res*. 2014;20(3):548-556.
2. Wu J, Liu C, Tsui ST, Liu D. Second-generation inhibitors of Bruton tyrosine kinase. *J Hematol Oncol*. 2016;9(1):80.
3. Tam CS, Opat S, Cull G, et al. Twice daily dosing with the highly specific BTK inhibitor, BGB-3111, achieves complete and continuous BTK occupancy in lymph nodes, and is associated with durable responses in patients (pts) with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma [ASH abstract 642]. *Blood*. 2016;128(suppl 22).
4. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31(1):88-94.

Integrated and Long-Term Safety Analysis of Ibrutinib in Patients With Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

Toxicity restricts chemotherapy regimens to a finite number of treatment cycles. In contrast, ibrutinib is associated with reduced toxicity and therefore is administered until disease progresses or unacceptable toxicity does occur. An integrated safety analysis was undertaken to evaluate the safety and tolerability of ibrutinib therapy in patients with relapsed or refractory CLL/SLL from 2 randomized phase 3 trials: RESONATE (PCYC-1112; A Phase 3 Study of Ibrutinib [PCI-32765] Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia) and RESONATE-2 (PCYC-1115; A Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma).[1-3] The RESONATE trial included 391 previously treated patients. The treatment arms were ibrutinib at 420 mg once daily (n=195) and ofatumumab at an initial dose of 300 mg followed by 2000 mg via 11 doses given throughout 24 weeks (n=196). In the ofatumumab arm, 132 patients crossed over to ibrutinib following disease progression. RESONATE-2 included 269 treatment-naive patients ages 65 years or older. The treatment arms were ibrutinib at 420 mg once daily (n=136) and chlorambucil at 0.5 mg/kg on days 1 and 15 in a 28-day cycle for a maximum of 12 cycles, with optional dose increases to a maximum of 0.8 mg/kg (n=133).

The integrated analysis included 330 patients who received ibrutinib treatment in RESONATE or RESONATE-2. Two-thirds of patients were male, 51% of patients had Rai stage III/IV disease at baseline, and 54% had bulky disease with a tumor measurement of at least 5 cm. Fifty-nine percent of patients had baseline cytopenias. Patients received ibrutinib for a median of 29.0 months (range, 0.2-42.9 months), and 16% of patients continued treatment for longer than 36 months. Concomitant treatments included CYP3 inhibitors (53%), antiplatelet agents (50%), anticoagulants (28%), packed red blood cell transfusions (6%), granulocyte growth factors (3%), and intravenous immunoglobulin (2%). Among the 38% of patients who discontinued treatment, the most common reasons were progressive disease (16%), AEs (11%), or death (5%). Discontinuations owing to an AE occurred in 19% of patients overall, and were highest in the first year of treatment, with 20, 10, and 7 discontinuations during years 1, 2, and 3, respectively. Similarly, dose reductions owing to an AE occurred in 13%

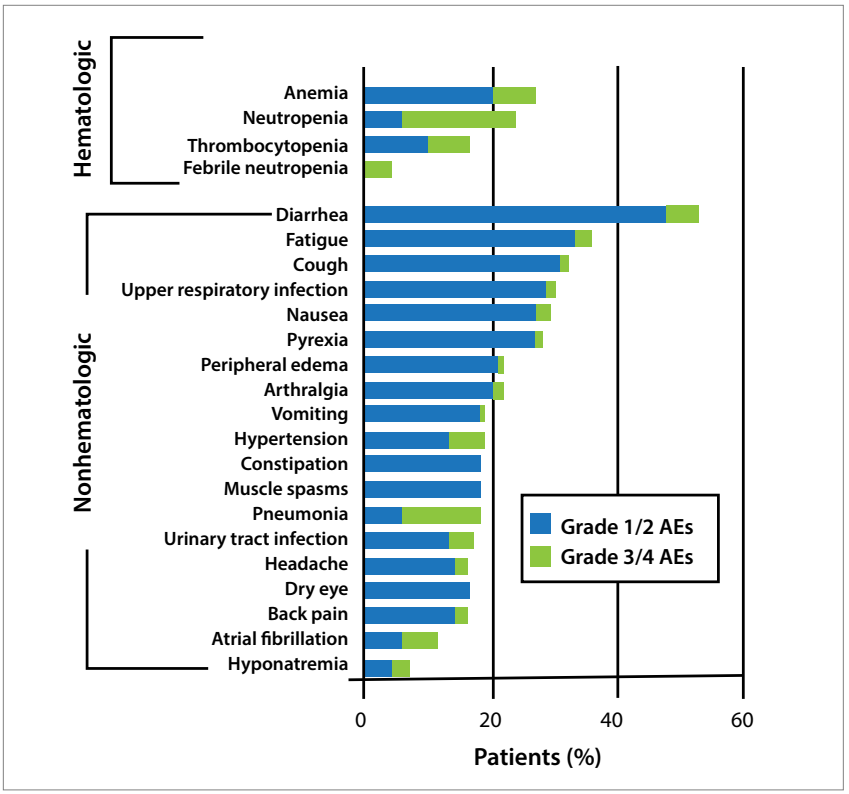

Figure 4. Adverse events (AEs) associated with ibrutinib in the RESONATE and RESONATE-2 trials. RESONATE, PCYC-1112; A Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia; RESONATE-2, PCYC-1115; A Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Adapted from Coutre S et al. ASH abstract 4383. *Blood*. 2016;128(suppl 22).[3]

of patients and were highest during the first year of treatment, with reductions reported in 23, 16, and 5 patients during years 1, 2, and 3, respectively.

The most common AEs of any grade were diarrhea (53%) and fatigue (36%; Figure 4). Other AEs of any grade reported in at least 25% of patients were upper respiratory tract infection (30%), nausea (29%), pyrexia (28%), and anemia (27%). Grade 3/4 AEs observed in at least 5% of patients included neutropenia (18%), pneumonia (12%), anemia (7%), and hypertension (6%). AEs leading to dose reduction in at least 3 patients included neutropenia and diarrhea, each occurring in 5 patients; atrial fibrillation, occurring in 4 patients; and anemia, thrombocytopenia, and arthralgia, each occurring in 3 patients. AEs leading to discontinuation in 2 or more patients included pneumonia in 4 patients, anemia and atrial fibrillation in 3 patients each, and diarrhea, subdural hematoma, and thrombocytopenia, each occurring in 2 patients. Of the 29 patients (9%) who died, the most common reason was progressive disease, reported in 8 patients, followed by pneumonia/lung infection, reported in 7 patients. AEs of particular clinical relevance included diarrhea, arthralgia, hypertension, rash, bleeding or bruising, fatigue, and atrial fibrillation. The majority of these AEs were of grade 1 or 2, and most resolved, with the exception of hypertension, which resolved in only 37% of cases. The median duration of these AEs was less than 35 days, with the exception of fatigue, which had a median of duration of 57 days. Rates of diarrhea, fatigue, rash, and grade 3/4 infections were highest during the first year of ibrutinib treatment, while rates of arthralgia and atrial fibrillation remained similar during years 1, 2, and 3 of treatment. In contrast, rates of hypertension increased with continued treatment; however, the majority of hypertensive events were ongoing or recurrent after 1 year of treatment.

In the same study, a long-term safety analysis was conducted on patients from the PCYC-1102 and PCYC-1103 trials who received ibrutinib therapy.[3] The 94 patients from these trials had a median follow-up of 47.9 months (range, 0.3-67.4 months). The most common grade 3/4 hematologic AEs were neutropenia (15%), thrombocytopenia (7%), and decreased lymphocyte count (6%). The most common grade 3/4 nonhematologic AEs were hypertension (30%), pneumonia (17%), and atrial fibrillation (11%). Reported secondary malignancies included basal cell carcinoma and squamous cell carcinoma in 4 patients each, and myelodysplastic syndrome in 2 patients.

References

1. Byrd JC, Brown JR, O'Brien S, et all; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
2. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
3. Coutre S, Byrd JC, Hillmen P, et al. Integrated and long-term safety analysis of ibrutinib in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). [ASH abstract 4383]. *Blood*. 2016;128(suppl 22).
4. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014;15(1):48-58.

Acalabrutinib Monotherapy in Patients With Ibrutinib Intolerance: Results From the Phase 1/2 ACE-CL-001 Clinical Study

Ibrutinib may be associated with AEs such as diarrhea, rash, atrial fibrillation, and bleeding, which may result from off-target effects.[1] Acalabrutinib (ACP-196) is a potent, second-generation inhibitor of BTK that binds irreversibly to the BTK kinase domain but has shown minimal activation of nontarget receptor pathways.[2,3] In kinase inhibition assays, the IC_{50} of acalabrutinib is greater than that of ibrutinib when tested against TEC (93 nM vs 7.0 nM), epidermal growth factor receptor (>1000 nM vs 5.3 nM), HER2/ERBB2 (~1000 nM vs 6.4 nM), interleukin-2–inducible T-cell kinase (>1000 nM vs 4.9 nM), and others. Dr Farrukh Awan presented results from the ibrutinib-intolerant patients enrolled in the ongoing, multinational phase 1/2 ACE-CL-001 trial, which investigated acalabrutinib monotherapy in patients with CLL/SLL.[4] Results have already been reported for the cohort of 60 patients with relapsed or refractory disease, showing an ORR of 95%, including 85% PRs and 10% PRs with lymphocytosis.[2] In addition, results from 72 treatment-naive patients yielded an ORR of 97%, including 87.5% PRs and 10% PRs with lymphocytosis.

The ibrutinib-intolerant cohort included adults with confirmed CLL who were intolerant to ibrutinib as determined by the investigator. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were excluded if their CLL involved the central nervous system or if they had significant cardiovascular disease.

Results of the Phase 3 Study of Lenalidomide Versus Placebo As Maintenance Therapy Following Second-Line Treatment for Patients With Chronic Lymphocytic Leukemia (the CONTINUUM Trial)

The randomized phase 3 CONTINUUM (A Study to Evaluate the Efficacy and Safety of Lenalidomide as Maintenance Therapy for Patients With B-Cell Chronic Lymphocytic Leukemia [CLL] Following Second Line Therapy) study evaluated lenalidomide vs placebo as maintenance therapy in previously treated CLL patients (Abstract 230). Eligible patients had achieved at least a PR on second-line therapy. Patients initially received lenalidomide at 2.5 mg daily, with escalation to 10 mg daily if the drug was well-tolerated. The 314 patients had a median age of 63 years (range, 37-84 years), and 47% of patients had 1 or more poor prognostic factors. After a median follow-up of 31.5 months, median PFS was significantly prolonged in patients who received lenalidomide maintenance therapy (33.9 months vs 9.2 months; HR, 0.40; 95% CI, 0.29-0.55; $P<.001$). In the lenalidomide vs the placebo arm, 35.7% and 58.4% of patients received subsequent therapy for their CLL. In these patients, median PFS was again significantly longer in patients treated with maintenance lenalidomide (57.5 months vs 32.7 months; HR, 0.46; 95% CI, 0.29-0.70; $P<.001$). No new safety signals were raised, and health-related quality of life was similar for patients receiving lenalidomide or placebo during the maintenance phase.

Table 1. Responses in Evaluable Patients Treated With Acalabrutinib Monotherapy

Best Response	N=29 (%)
CR	1 (3.4)
PR	15 (51.7)
PRL	7 (24.1)
SD	6 (20.7)
ORR (CR + PR), n (%)	16 (55.2) 95% CI, 35.7-73.6
ORR (CR + PR + PRL), n (%)	23 (79.3) 95% CI, 60.3-92.0

CR, complete response; ORR, overall response rate; PR, partial response; PRL, partial response with lymphocytosis; SD, stable disease.

Adapted from Awan FT et al. ASH abstract 638. *Blood*. 2016;128(suppl 22).[4]

Thirty patients received acalabrutinib at 100 mg twice daily and 3 received acalabrutinib at 200 mg daily. The data cutoff was September 1, 2016. The primary objective was safety, including frequency, severity, and attribution of AEs, with secondary objectives of ORR, duration of response, and PFS. The 33 enrolled patients had a median age of 64 years (range, 50-82 years), and 61% were male. Thirty-one percent of patients had Rai stage III/IV disease, and 78% had bulky disease with a tumor diameter of at least 5 cm. Patients had received a median of 4 prior therapies (range, 2-13). Most patients (91%) had received ibrutinib as their most recent prior therapy, and the median duration of prior ibrutinib treatment was 11.5 months (range, 1-62 months). Baseline cytopenias were present in 78% of patients. Genomic risk factors included del(11q), del(17p), and unmutated *IgHV* in 31%, 38%, and 81% of patients, respectively. The most common AEs of any grade reported during ibrutinib treatment included rash (21%), arthralgia (18%), diarrhea (12%), and fatigue (12%).

The median time on acalabrutinib was 12.2 months (range, 0.2-23.6 months). Twenty-four patients (73%) remained on acalabrutinib therapy. Reasons for discontinuation included progressive disease (9%), AEs (9%), and physician decision (3%). AEs leading to discontinuation included 1 patient with hemorrhagic stroke resulting in death, 1 patient with fungal infection leading to death, and 1 patient who was diagnosed with metastatic endometrial cancer. Twelve patients (36%) had previously experienced an AE with ibrutinib that recurred during treatment with acalabrutinib. Only 2 of these events increased in severity, rising from grade 1 to grade 2. No patients discontinued acalabrutinib owing to a previous ibrutinib-related AE.

The most common AEs of any grade in the 33 patients treated with acalabrutinib included diarrhea (52%), headache (39%), cough (24%), and increased weight (24%). Grade 3/4 AEs occurring in at least 2 patients included thrombocytopenia in 9% of patients, and anemia, neutropenia, pneumonia, hypertension, and paresthesia, each occurring in 6% of patients. Serious AEs occurred in 11 patients (33%). Two atrial fibrillation events were reported: 1 grade 2 and 1 grade 3. Both were considered unrelated to study drug by the investigator. The 2 grade 5 events included 1 each of hemorrhagic stroke and disseminated systemic fungal infection, and these were also considered unrelated to study drug by the investigators.

In the 29 patients evaluable for a response, the ORR was 79.3% (95% CI, 60.3%-92.0%), including 1 patient (3.4%) with a CR, 15 (51.7%) with a PR, and 7 (24.1%) with a PR with lymphocytosis (Table 1). The median time until achievement of PR with lymphocytosis or better was 1.9 months, and response duration was at least 12 months in 81% of respond-

ing patients. Median PFS was not yet reached. An ongoing phase 2 study (A Study of ACP-196 [Acalabrutinib] in Subjects With Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy) is evaluating acalabrutinib monotherapy in patients with relapsed refractory CLL and ibrutinib intolerance.[5]

References

1. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol*. 2015;1(1):80-87.
2. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323-332.
3. Wu J, Liu C, Tsui ST, Liu D. Second-generation inhibitors of Bruton tyrosine kinase. *J Hematol Oncol*. 2016;9(1):80.
4. Awan FT, Schuh A, Brown JR, et al Acalabrutinib monotherapy in patients with ibrutinib intolerance: results from the phase 1/2 ACE-CL-001 clinical study [ASH abstract 638]. *Blood*. 2016;128(suppl 22).
5. ClinicalTrials.gov. A study of ACP-196 (acalabrutinib) in subjects with relapsed/refractory CLL and intolerant of ibrutinib therapy. Identifier: NCT02717611. https://clinicaltrials.gov/ct2/show/NCT02717611. Accessed December 13, 2016.

Updated Efficacy and Safety From the Phase 3 RESONATE-2 Study: Ibrutinib as First-Line Treatment Option in Patients 65 Years and Older With Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

Because CLL/SLL occurs predominantly in the elderly, the patient population is marked by increased comorbidities that limit the aggressiveness of treatment. Ibrutinib is associated with favorable tolerability and enables treatment without chemotherapy. Dr Paul Barr presented updated efficacy and safety data from the phase 3 RESONATE-2 trial, which evaluated first-line ibrutinib vs chlorambucil in elderly patients with CLL/SLL.[1,2] The study enrolled 269 patients ages 65 years or older with treatment-naive CLL/SLL who were not candidates for fludarabine-based therapy. Patients with del(17p) were ineligible. After stratification for performance status and disease stage, patients were randomly assigned to receive ibrutinib at 420 mg once daily until disease progression or unacceptable toxicity, or chlorambucil at 0.5 mg/kg up to a maximum of 0.8 mg/kg on days 1 and 15 in 28-day cycles for a maximum of 12 cycles until disease progression, unacceptable toxicity, or lack of efficacy. Patients with progressive disease were enrolled in a separate extension study (PCYC-1116-CA) with treatment based on investigator choice. The updated analysis of data from 269 patients therefore included 55 patients from the chlorambucil arm who experienced disease progression and underwent subsequent treatment with ibrutinib.

The 269 patients had a median age of 73 years (range, 65-90 years), and 45% had Rai stage III/IV disease. Thirty-five percent of patients had bulky disease, with a tumor diameter of 5 cm or greater, and 57% had an ECOG performance status of 1 or 2. Del(11q) was observed in 20% of patients, and unmutated *IgHV* in 44%. Comorbidities included a Cumulative

Venetoclax (VEN) Monotherapy for Patients With Chronic Lymphocytic Leukemia (CLL) Who Relapsed After or Were Refractory to Ibrutinib or Idelalisib

Venetoclax monotherapy was evaluated in a phase 2 study of patients with relapsed or refractory CLL after treatment with ibrutinib or idelalisib (Abstract 637). Venetoclax treatment was initiated at 20 mg daily with stepwise escalation over 5 weeks to the final dose of 400 mg daily. As of June 10, 2016, 43 patients with prior ibrutinib were enrolled into arm A, and 21 patients with prior idelalisib were enrolled into arm B. Patients had a median age of 67 years (range, 48-85 years), and 86% had unmutated *IgHV*. In arm A, 49% had del(17p) vs 10% in arm B. The 64 patients received venetoclax for a median of 9 months (range, 1.3-16 months). In arm A vs arm B, 42% vs 19% of patients discontinued treatment, 44% vs 33% of patients had dose interruptions, and 16% vs 10% of patients had dose reductions, respectively. Based on independent assessment, the ORR in arm A was 70%, including 2% CRs and 67% PRs. In arm B, the ORR was 62%, all of which were PRs. After 12 months of follow-up, median PFS and median OS had not been reached, reflecting durable responses. Between weeks 24 to 48, 45% of patients had peripheral blood samples that were negative for minimal residual disease. Venetoclax monotherapy was generally well-tolerated.

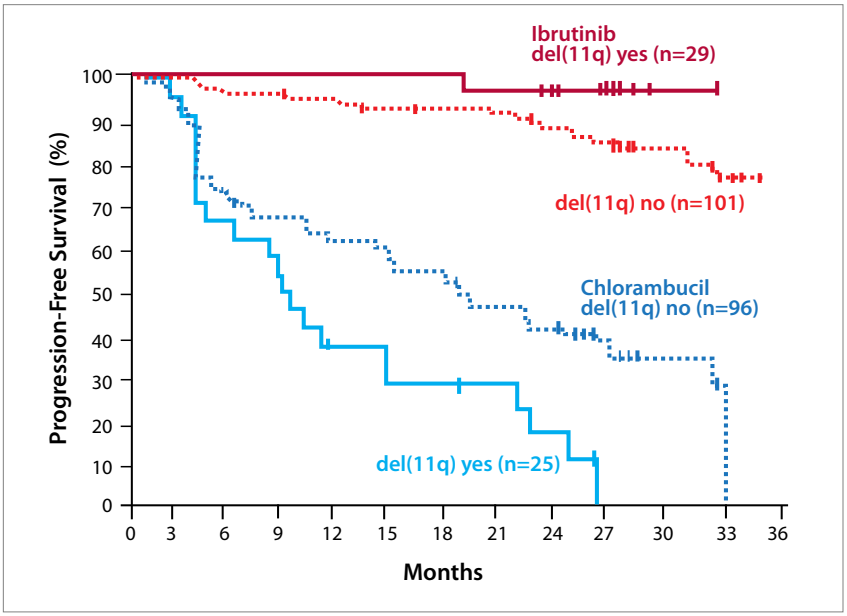

Figure 5. The estimated 24-month progression-free survival according to deletion 11q status in the RESONATE-2 trial. RESONATE-2, PCYC-1115; A Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Adapted from Barr PM et al. ASH abstract 234. *Blood*. 2016;128(suppl 22).[2]

Illness Rating Scale for Geriatrics score of greater than 6 in 32%, creatinine clearance of less than 60 mL/min in 47%, hemoglobin level of 11 g/dL or lower in 39%, and platelet count of 100 × 10^9/L or lower in 24% of patients. After 29 months of follow-up, the PFS was significantly improved in patients treated with ibrutinib (89 months vs 34 months; hazard ratio [HR], 0.121; 95% CI, 0.074-0.198; *P*<.0001). In the subgroup of patients with del(11q), ibrutinib treatment was associated with a 99% reduction in the risk of progression or death compared with chlorambucil (HR, 0.014; 95% CI, 0.002-0.108; *P*<.001; Figure 5). In patients without del(11q), ibrutinib conferred an 82% reduction in the risk of progression or death vs chlorambucil (HR, 0.180; 95% CI, 0.106-0.303; *P*<.0001). Ibrutinib treatment was associated with a 92% risk reduction in patients with unmutated *IgHV* (*P*<.0001) and an 83% risk reduction in patients with mutated *IgHV* (*P*<.001).

For the entire study population, 24-month OS was 95% with ibrutinib vs 84% with chlorambucil. These results confirmed the original findings that yielded an estimated 24-month PFS of 98% with ibrutinib vs 85% with chlorambucil, and a risk reduction of 84% with ibrutinib compared with chlorambucil (*P*=.001).[1] The 136 patients in the ibrutinib arm had an ORR of 92%, including 18% CRs or CRs with incomplete blood count recovery; 1% nodular PRs, indicating persistent nodules in the bone marrow; 71% PRs; and 1% PRs with lymphocytosis. CR rates improved with continued ibrutinib treatment, increasing from 7% at 12 months of follow-up, to 15% at 24 months, to 18% at 29 months. The ORR was 100% in patients with del(11q) vs 90% in those without, and 95% in patients with unmutated *IgHV* vs 88% in those without. With ibrutinib treatment, sustained improvement in the hemoglobin level was achieved in 90% of anemic patients vs 45% with chlorambucil (*P*<.0001). In patients with thrombocytopenia, a sustained improvement in platelet levels was achieved in 80% of those treated with ibrutinib vs 46% of those treated with chlorambucil (*P*=.0055).

The median duration of ibrutinib treatment was 29 months (range, 1-36 months), and 79% of patients were continuing treatment with ibrutinib at the time the study was reported. Among the 21% of patients who discontinued treatment, the reasons included AEs (12%), death (4%), disease progression (3%), and withdrawal of consent (1%). In patients treated with ibrutinib, the most common AEs of any grade included diarrhea (45%), fatigue (33%), and cough (28%). Anemia, nausea, peripheral edema, arthralgia, and pyrexia of any grade were observed in 20% to 23% of patients. Among patients treated with ibrutinib, major hemorrhage occurred in 7% and atrial fibrillation in 10%. During the 29 months of follow-up, AEs of grade 3 or greater included neutropenia (12%), pneumonia (7%), anemia (7%), hypertension (5%), hyponatremia (4%), and atrial fibrillation (4%). The majority of treatment-emergent AEs of grade 3 or greater occurred during the first year of treatment. However, atrial fibrillation of grade 3 or greater was reported in 1% of patients during the first year of treatment with ibrutinib and in 4% of patients during the third year of treatment. Rates of dose reduction and discontinuation owing to an AE also decreased over time.

References

1. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
2. Barr PM, Robak T, Owen CJ, et al. Updated efficacy and safety from the phase 3 RESONATE-2 study: ibrutinib as first-line treatment option in patients 65 years and older with chronic lymphocytic leukemia/small lymphocytic leukemia [ASH abstract 234]. *Blood*. 2016;128(suppl 22).

Updated Analysis of Overall Survival in Randomized Phase III Study of Idelalisib in Combination With Bendamustine and Rituximab in Patients With Relapsed/Refractory CLL

The treatment landscape for patients with relapsed or refractory CLL remains limited. Idelalisib is a selective, orally available, first-in-class, reversible inhibitor of phosphatidylinositol-4,5-bisphosphate 3-kinase delta (PI3Kδ) and represents an alternative to ibrutinib for disrupting B-cell receptor–mediated signal transduction. The PI3K family of enzymes mediates numerous cellular functions, including growth, motility, homing, retention, and adhesion. In the B-cell receptor pathway, PI3Kδ controls survival, proliferation, and chemokine secretion and is constitutively overexpressed in the B cells of CLL patients. Early experiments demonstrated the ability of idelalisib to induce apoptosis in primary CLL cells ex vivo while retaining activity in the presence of stromal cells.[1] It is approved in combination with rituximab for the treatment of relapsed CLL in patients ineligible for rituximab monotherapy based on comorbidities.[2]

Dr Andrew Zelenetz presented updated results from GS-US-312-0115 (A Randomized, Double-Blind and Placebo-Controlled Study of Idelalisib in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia [CLL]), which examined the addition of idelalisib to bendamustine plus rituximab.[3,4] The randomized, placebo-controlled, double-blind, phase 3 study enrolled adult CLL patients whose prior therapy included a purine analogue, bendamustine, or an anti-CD20 antibody and whose disease progressed within 36 months of completion of the last prior therapy. Among patients previously treated with bendamustine, this therapy ended at least 6 months before study enrollment. Patients with disease refractory to bendamustine were ineligible.

All patients received bendamustine at 70 mg/m^2 on days 1 and 2 and rituximab at 375 mg/m^2 on day 1 of cycle 1 followed by 500 mg/m^2 on day 1 of cycles 2 through 6. In addition to this regimen, patients were randomly assigned to receive idelalisib at 150 mg twice daily or placebo. Treatment with idelalisib or placebo was continued until disease progression, intolerable toxicity, withdrawal of consent, or death. Stratification factors included del(17p) and/or *TP53* mutation, *IgHV* mutation, and relapsed or refractory disease. The primary endpoint was PFS, with secondary endpoints of ORR, nodal response, OS, and CR.

The baseline characteristics were well-balanced between the 2 arms. The original study population of 416 patients had a median age of 63 years (range, 32-83 years), and 76% were male. Forty-five percent of patients had Rai stage III/IV disease. Patients had a median of 2 prior treatment regimens (range, 1-13), and the most common prior regimens were fludarabine, cyclophosphamide, and rituximab (67%), fludarabine and cyclophosphamide (22%), and chlorambucil (18%). More patients in the idelalisib arm had received prior bendamustine (15% vs 8%). Thirty-three percent of patients had del(17p) or *TP53* mutation, 83% had unmutated *IgHV*, and one-third had refractory disease.

After a median of 21 months of

ABSTRACT SUMMARY Nivolumab Combined With Ibrutinib for CLL and Richter Transformation: A Phase II Trial

An investigator-initiated phase 2 trial evaluated nivolumab, a PD-1 checkpoint inhibitor, plus ibrutinib in patients with relapsed or refractory CLL or Richter's transformation (Abstract 59). Patients in cohort 1 received initial treatment with nivolumab (3 mg/kg) every 2 weeks, with daily ibrutinib (420 mg) added after cycle 1. Patients in cohort 2 had a PR from ibrutinib treatment. These patients were already receiving daily ibrutinib (420 mg); nivolumab (3 mg/kg every 2 weeks) was added to the regimen. Thirteen patients were enrolled, including 5 with CLL and 5 with Richter's transformation in cohort 1, and 5 with CLL in cohort 2. No immune-related AEs of grade 3 or higher occurred, and no patients discontinued treatment owing to an AE. Among the 5 CLL patients in cohort 1, 1 patient with del(13q) who had received prior treatment with ofatumumab achieved a CR lasting beyond 10 months, 3 patients achieved a PR lasting from 7+ months to greater than 9 months, and 1 patient showed no response. Of the 5 patients with CLL in cohort 2, 2 discontinued from the study and 3 showed stable disease. Of the 5 patients with Richter transformation in cohort 1, 2 discontinued from the study, 2 showed a CR for Richter's transformation and a PR for CLL, and 1 patient showed a PR for CLL.

follow-up, more patients remained on study in the idelalisib arm (34%) than the placebo arm (11%), and 31% vs 0 patients continued on study treatment, respectively. After the initial prespecified interim analysis, patients in the placebo arm were informed and discontinued treatment. The updated analysis demonstrated a significant improvement in survival with idelalisib, with a median OS of not reached vs 40.6 months for placebo (HR, 0.67; 95% CI, 0.47-0.96; *P*=.04). PFS based on independent review was also significantly improved with idelalisib (23.0 months vs 11.1 months; HR, 0.31; 95% CI, 0.24-0.41; *P*<.0001). In the subgroup of patients without del(17p) or *TP53* mutation, the median PFS was 27.8 months in the idelalisib arm vs 11.2 months in the placebo arm (HR, 0.25; 95% CI, 0.17-0.35; *P*<.001). Further subgroup analysis favored the inclusion of idelalisib, although many of these subgroups included few patients.

Safety findings were similar to those previously reported. An AE of grade 3 or greater occurred in 95% of the idelalisib arm vs 78% of the placebo arm, and 71% vs 45% of patients experienced a serious AE, respectively. AEs leading to dose reduction occurred in 16% vs 6% of patients, AEs leading to discontinuation occurred in 33% vs 15%, and deaths occurred in 12% vs 9% of patients in the idelalisib vs placebo arms, respectively. Grade 3/4 AEs of interest that occurred with greater frequency in the idelalisib arm included neutropenia (60% vs 47%), febrile neutropenia (24% vs 6%), diarrhea (12% vs 2%), and increased alanine transaminase (11% vs <1%). The most common serious AEs in the idelalisib vs placebo arms were febrile neutropenia (21% vs 5%), pneumonia (17% vs 8%), and pyrexia (12% vs 5%).

Concerns have been raised regarding rates of infection in patients treated with idelalisib. Infection with *Pneumocystis jirovecii* pneumonia was observed in 4 patients (2%) in the idelalisib arm vs 0 patients in the placebo arm, and cytomegalovirus infection was observed in 13 patients (6%) vs 3 (1%), respectively. However, the only death from these infections occurred in a patient with cytomegalovirus infection in the placebo arm. The risk of cytomegalovirus infection decreased over time in both arms. Grade 3/4 alanine or aspartate transaminase elevations were more common in patients treated with idelalisib (21% vs 3% and 16% vs 3%, respectively).

References

1. Herman SE, Gordon AL, Wagner AJ, et al. Phosphatidylinositol 3-kinase-δ inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. *Blood*. 2010;116(12):2078-2088.
2. Zydelig [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016.
3. Zelenetz AD, Brown JR, Delgado J, et al. Updated analysis of overall survival in randomized phase III study of idelalisib in combination with bendamustine and rituximab in patients with relapsed/refractory CLL [ASH abstract 231]. *Blood*. 2016;128(suppl 22).
4. Zelenetz AD, Robak T, Coiffier B, et al. Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia: results of a phase 3 randomized double-blind placebo-controlled study [ASH abstract LBA-5]. *Blood*. 2015;126(suppl 23).

CLL2-BIG – A Novel Treatment Regimen of Bendamustine Followed By GA101 and Ibrutinib Followed by Ibrutinib and GA101 Maintenance in Patients With Chronic Lymphocytic Leukemia (CLL): Results of a Phase II-Trial

Obinutuzumab (GA101) is a humanized, glycoengineered, anti-CD20 antibody. In preclinical studies, obinutuzumab was superior to rituximab in the ability to induce direct cell death and antibody-dependent cellular cytotoxicity, with reduced dependency on complement.[1] In a phase 3 trial of 781 patients, the combination of chlorambucil plus an anti-CD20 antibody was superior to chlorambucil alone in CLL patients with comorbidities.[2] Dr Julia von Tresckow presented results from the CLL2-BIG (Sequential Regimen of Bendamustine [B] Followed by GA101 and Ibrutinib [I] in CLL Patients) trial.[3] The prospective, open-label, multicenter, phase 2 trial investigated sequential treatment with bendamustine for initial debulking followed by induction and maintenance treatment with obinutuzumab and ibrutinib. A high tumor burden was defined by

ABSTRACT SUMMARY Optimal Sequencing of Ibrutinib, Idelalisib, and Venetoclax in CLL: Results From a Large Multi-Center Study of 683 US-Patients

A large retrospective analysis of CLL patients treated with kinase inhibitors was conducted to determine optimal sequencing and identify patterns of failure (Abstract 4400). Investigators identified 621 patients treated with ibrutinib and 62 treated with idelalisib as their first kinase. The efficacy of agent sequencing was evaluated in patients who had received initial treatment with a kinase inhibitor followed by treatment with a different kinase inhibitor or venetoclax. Patients who received any kinase inhibitor followed by venetoclax had an ORR of 74%, including 32% CRs and 42% PRs or PRs with lymphocytosis. Patients who received idelalisib followed by ibrutinib had an ORR of 75%, including 5% CRs and 70% PRs or PRs with lymphocytosis. Patients who received ibrutinib followed by idelalisib had the lowest ORR of 46%; no patients achieved a CR, and 46% achieved PRs or PRs with lymphocytosis. Patients who received ibrutinib as their first kinase regimen compared with idelalisib had a superior PFS in all settings, including first-line, relapsed or refractory disease, clinical trials, and commercial use. Patients with genetic risk factors also showed an improved PFS when ibrutinib was the first kinase inhibitor.

Table 2. Outcome Among Patients Who Underwent Debulking With Bendamustine

Response	Frontline (%)	Relapsed/ Refractory	n (%)
Unconfirmed CR	1 (3.7)	3 (17.6)	4 (9.1)
Unconfirmed CR with incomplete recovery of the bone marrow	2 (7.4)	1 (5.9)	3 (6.8)
PR	15 (55.6)	7 (41.2)	22 (50.0)
SD	6 (22.2)	5 (29.4)	11 (25.0)
PD	1 (3.7)	1 (5.9)	2 (4.5)
Missing response	2 (7.4)	0	2 (4.5)
ORR	66.7	64.7	65.9

CR, complete remission; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

Adapted from von Tresckow J et al. ASH abstract 640. *Blood*. 2016;128(suppl 22).[3]

an absolute lymphocyte count greater than 25,000 cells/μL and/or lymph node measurement of 5 cm or greater, and these patients received 2 cycles of bendamustine at 70 mg/m^2 on days 1 and 2 prior to induction. Patients received 6 cycles of induction treatment with obinutuzumab and ibrutinib, followed by maintenance therapy with ibrutinib and obinutuzumab every 3 months for up to 24 months or until they achieved a CR (as shown by absence of minimal residual disease). Two cycles of debulking with bendamustine were given before the start of the induction period in patients with an initial high tumor burden. The primary endpoint is the ORR 3 months after the start of the last induction cycle. Secondary endpoints included the ORR after debulking, minimal residual disease, and safety.

Sixty-six patients were enrolled between January 2015 and August 2015. Five patients completed fewer than 2 induction cycles and were excluded from the analysis. The 61 patients included in the analysis had a median age of 66 years (range, 36-83 years), with 51% of patients older than 65 years. Thirty patients were treatment-naive, and 31 had relapsed or refractory CLL. All patients had an ECOG performance status of 0 or 1. Fifty-seven percent of patients were male, and the median time from initial diagnosis was 56.5 months (range, 1.2-222.8 months). Patients had Binet stage A (26.2%), B (37.7%), or C (36.1%) disease, and the median Cumulative Illness Rating Scale score was 3 (range, 0-11). The median creatinine clearance rate was 76.5 mL/min (range, 33.1-154.7 mL/min). The genetic risk factors unmutated *IgHV*, del(11q), and del(17p) were present in 70.0%, 23.0%, and 13.1% of patients, respectively. Other genetic risk factors included del(13q) in 50.8% of patients, trisomy 12 in 19.7% of patients, and *TP53* deletion in 19.7% of patients.

Forty-four patients underwent debulking with bendamustine, including 27 treatment-naive patients and 17 with relapsed or refractory disease. Bendamustine yielded an ORR of 65.9%, including 4 patients (9.1%) with an unconfirmed CR, 3 (6.8%) with an unconfirmed CR with incomplete bone marrow recovery, and 22 (50.0%) with a PR (Table 2). Among the 61 patients who underwent induction treatment, 1 patient with a documented PR died after the fifth treatment course owing to duodenitis/defense weakness related to study therapy. The ORR in 61 patients was 100% by investigator assessment, including unconfirmed CRs in 25 (41%), unconfirmed CRs with incomplete bone marrow recovery in 3 (4.9%), and PRs in 33 (54.1%). Based on flow cytometry analysis of peripheral blood, 29 patients (47.5%)

achieved negative minimal residual disease at final restaging, including 19 patients with an unconfirmed CR, 1 patient with an unconfirmed CR and incomplete bone marrow recovery, and 9 patients with a PR. The most common grade 3/4 AEs included neutropenia (14.8%), thrombocytopenia (13.1%), infusion-related reactions (4.8%), and pneumonia (3.3%).

References

1. Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. *Mol Cancer Ther*. 2013;12(10):2031-2042.
2. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
3. von Tresckow J, Cramer P, Bahlo J, et al. CLL2-BIG–a novel treatment regimen of bendamustine followed by GA101 and ibrutinib followed by ibrutinib and GA101 maintenance in patients with chronic lymphocytic leukemia (CLL): results of a phase II-trial [ASH abstract 640]. *Blood*. 2016;128(suppl 22).

Highlights in Chronic Lymphocytic Leukemia From the 2016 American Society of Hematology Annual Meeting and Exposition: Commentary

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The 2016 American Society of Hematology (ASH) Annual Meeting featured several important abstracts on chronic lymphocytic leukemia (CLL). Long-term follow-up analyses were presented for clinical trials of ibrutinib. Other studies examined BGB-3111, a new Bruton tyrosine kinase (BTK) inhibitor, and idelalisib in combination with bendamustine and rituximab.

Ibrutinib

I presented an analysis of the 5-year experience with ibrutinib.[1] These data are important because they represent the longest follow-up available for ibrutinib. The analysis was based on data from the original phase 1b/2 study, which included 2 cohorts: 31 previously untreated patients ages 65 years or older, and 101 patients with relapsed/refractory disease, who had received a median of 4 prior therapies.[2] The relapsed/refractory patients were therefore heavily pretreated. The follow-up analysis shows a best response of 89% for both groups together. In the treatment-naive patients, the complete response (CR) rate was 29%, which reflects a slight improvement from the 26% that was reported for this group in 2015.

This 5-year analysis provided several new findings concerning progression-free survival (PFS). In previous studies of ibrutinib, the median PFS had not been reached for all patients. The only subgroup with a median PFS had been relapsed/refractory patients with del(17p), in whom it was 26 months. A new finding from the 5-year data is a median PFS of 52 months in the overall relapsed/refractory setting. The median PFS for patients with the del(11q) is 55 months. Among patients who do not have either of these high-risk abnormalities—del(17p) or del(11q)—the median PFS has still not been reached, which is quite striking at 5 years, especially given that the median number of prior regimens in these patients was 4. Median overall survival was reached in only one group of patients, relapsed/refractory patients with del(17p), in whom it was 57 months.

Among treatment-naive patients, the survival curve had been very similar

for years. There had been 1 early drop in the curve, which reflected a patient who progressed and died within the first year of the study. The 5-year analysis shows another late drop in the curve just before 5 years, which represents a patient in remission who died of a secondary malignancy. Among the original 31 treatment-naive patients, only a couple have come off study. Only 1 patient has progressed. The 5-year PFS in the treatment-naive cohort is 96%. These data are very striking.

An analysis was performed to identify any factors that might predict overall survival or PFS and included previous lines of prior therapy and complex karyotype. A multivariate analysis of the relapsed/refractory patients showed that the relevant predictor was the del(17p), which shortened both PFS and overall survival.

Dr Paul Barr presented updated efficacy and safety data from the phase 3 RESONATE-2 trial (PCYC-1115; A Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma).[3,4] This randomized trial led to the approval of ibrutinib as frontline therapy in the United States. Patients were randomly assigned to receive the standard dose of ibrutinib, 420 mg daily, or chlorambucil. Patients were older than 70 years, or ages 65 to 70 years with comorbidities; their median age was 72 years. Chlorambucil was a reasonable comparator arm in this older population. The results, as reported in 2015 in the *New England Journal of Medicine*, showed that PFS was dramatically longer with ibrutinib than with chlorambucil.[4] The updated data presented by Dr Barr continued to show a dramatic difference. Median PFS was not yet reached with ibrutinib vs 15 months with chlorambucil. The 24-month PFS was 89% with ibrutinib. Even though crossover was allowed on this trial, there was still a survival advantage in the ibrutinib arm.

A subset analysis evaluated the impact of del(11q) and mutated vs unmutated immunoglobulin heavy chain variable (*IgHV*). The relevance of this analysis is not focused on response. It is known that with chemotherapy-based regimens, response rates are similar regardless of whether patients have del(11q) or unmutated *IgHV*. Progression-free survival, however, is significantly shorter in patients with del(11q) or unmutated *IgHV*. This difference was seen in the chlorambucil arm in this study. Among patients treated with chlorambucil, those with the del(11q) had a shorter PFS than those without del(11q). Similarly, patients with unmutated *IgHV* had a shorter PFS than those without the mutation when treated with chlorambucil. These differences were not seen in the ibrutinib cohort. The entire ibrutinib cohort had a high response rate of 92%. In addition, the CR rate increased from 7% at 1 year to 18% at 2 years. Based on the phase 2 data, the CR rate could potentially improve with time.

The adverse events (AEs) reported for ibrutinib were as expected. Even though the population was older, 16 patients (approximately 12%) discontinued treatment owing to AEs. It is good to know that the longer follow-up is showing robust data with ibrutinib in the frontline setting.

When interpreting these results, some physicians might mention that the current standard of care is to use chlorambucil plus an antibody, rather than chlorambucil alone. However, the median PFS was only 26 months in the randomized trial that led the US Food and Drug Administration (FDA) to approve obinutuzumab with chlorambucil as a frontline regimen,[5] which is far shorter than that achieved with ibrutinib. Therefore, the results of RESONATE-2 are not negated by the use of chlorambucil without an antibody.

BGB-3111

BGB-3111, a new oral agent, is a BTK inhibitor. It is very potent against BTK and has higher IC_{50} for some of the other kinases that ibrutinib targets. For example, it has a higher IC_{50} for the epidermal growth factor receptor (EGFR), which could theoretically translate into less likelihood of rash or diarrhea compared to that seen with other BTK inhibitors. It has a much higher IC_{50} for IL2 inducible T-cell kinase (ITK) than ibrutinib, so potentially it will not interfere with the activities of antibodies. The IC_{50} on TEC, however, appears similar between BGB-3111 and ibrutinib, which is important because TEC may be responsible for the atrial fibrillation and bleeding that can be seen with ibrutinib. It would be ideal to have a BTK inhibitor that does not target TEC, such as the novel agent acalabrutinib.[6]

Dr Constantine Tam presented interim results of an ongoing phase 1 study of BGB-3111.[7] The study evaluated a variety of different doses ranging from 40 mg daily to 160 twice daily. The study showed that higher plasma levels are achieved with the standard dose of BGB-3111, and they were associated with activity. An interesting aspect of this study is that it looked within the lymph nodes to determine BTK occupancy. The optimal dose of ibrutinib, 420 mg daily, was selected because it resulted in almost complete occupancy of BTK in the peripheral blood mononuclear cells. The lymph nodes, however, were not evaluated when determining this dose. This information might be relevant because there are some data suggesting that patients with bulky adenopathy do not have as sustained a PFS with ibrutinib. In the study of BGB-3111, the lymph nodes had a sustained occupancy above 90% at doses of 160 twice daily or 320 daily.

The interim analysis provided data for 46 of 63 CLL/SLL patients.

The most common side effects with BGB-3111 were petechiae, purpura, and contusion, suggesting that the low IC_{50} for TEC may lead to minor bleeding, similar to that seen with ibrutinib. Diarrhea, however, was much less frequent than with ibrutinib, occurring in only 20% of patients. There was 1 episode of serious hemorrhage, and 1 episode of atrial fibrillation. The response rate was 96%, which is quite good, especially considering that the patients in the study had relapsed/refractory disease. These patients also showed improvements in cytopenias. Among the relapsed/refractory patients, the median number of prior regimens was 2, so they were less heavily pretreated than patients in the ibrutinib trials previously discussed. No patient has yet developed progressive disease, and there have been no reports of Richter's transformation. These data are encouraging.

Idelalisib in Combination With Bendamustine and Rituximab

Dr Andrew Zelenetz presented an updated analysis of overall survival in a randomized, placebo-controlled, phase 3 trial of idelalisib added to bendamustine and rituximab (BR) in patients with relapsed/refractory CLL.[8] Previous data for this study were presented at the 2015 ASH meeting.[9] The new analysis is based on a longer median follow-up of 21 months. This study shows a survival benefit when idelalisib is added to bendamustine and rituximab. Median overall survival was 40.6 months in the placebo arm—patients who received BR without idelalisib—and was not reached in the idelalisib plus BR arm. The difference was statistically significant. This survival advantage is a new finding. The PFS continues to be very different, at a median of 11 months with placebo vs 23 months with idelalisib. This improvement was seen in basically all subgroups. An analysis that removed the patients with *17p* or *TP53* mutation showed that the median PFS did not change in the placebo arm, but increased to up to 28 months in the idelalisib arm.

In terms of AEs, more febrile neutropenia was seen with idelalisib than placebo. In the idelalisib group, 24% of patients experienced grade 3 or higher febrile neutropenia, vs only 6% in the placebo group. There was more transaminitis in the idelalisib arm, as is seen in single-agent use. There was also more pneumonia among patients who received idelalisib, at 17% vs 8%. Four cases of *Pneumocystis jirovecii* pneumonia (PJP) occurred in the idelalisib plus BR arm, vs none in the placebo/BR arm. There were 13 cases of cytomegalovirus (CMV) in the idelalisib plus BR arm and only 3 in the placebo plus BR arm. In March 2016, the FDA closed the frontline trials of idelalisib based on a higher incidence of infection. Most of that patient population received BR plus idelalisib as initial therapy. Thus, it was the same regimen in the frontline setting that led to the closing of the frontline studies. Similarly, in the current analysis, there were more cases of PJP and CMV, but the majority of the infections were not atypical. In addition, despite these infections, there was still a significant survival advantage in favor of the idelalisib/BR arm.

Disclosure

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

References

1. O'Brien SM, Furman RR, Coutre SE, et al. Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia [ASH abstract 233]. *Blood*. 2016;128(suppl 22).
2. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014;15(1):48-58.
3. Barr PM, Robak T, Owen CJ, et al. Updated efficacy and safety from the phase 3 RESONATE-2 study: ibrutinib as first-line treatment option in patients 65 years and older with chronic lymphocytic leukemia/small lymphocytic leukemia [ASH abstract 234]. *Blood*. 2016;128(suppl 22).
4. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
5. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
6. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323-332.
7. Tam CS, Opat S, Cull G, et al. Twice daily dosing with the highly specific BTK inhibitor, BGB-3111, achieves complete and continuous BTK occupancy in lymph nodes, and is associated with durable responses in patients (patients) with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma [ASH abstract 642]. *Blood*. 2016;128(suppl 22).
8. Zelenetz AD, Brown JR, Delgado J, et al. Updated analysis of overall survival in randomized phase III study of idelalisib in combination with bendamustine and rituximab in patients with relapsed/refractory CLL [ASH abstract 231]. *Blood*. 2016;128(suppl 22).
9. Zelenetz AD, Robak T, Coiffier B, et al. Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia: results of a phase 3 randomized double-blind placebo-controlled study [ASH abstract LBA-5]. *Blood*. 2015;126(suppl 23).


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