SPECIAL ISSUE: **ASH MEETING RECAP**

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

25 YEARS
RESEARCH & LEADERSHIP

Evidence-Based ONCOLOGY™

JANUARY 2020
VOL. 26 • NO. 1

HIGHLIGHTS FROM THE MEETING

AJMC® Managed Markets Network®

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

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

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

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

Monitor complete blood counts monthly.

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

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

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

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

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

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

Monitor patients closely and treat as appropriate.

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LEADING THE WAY WITH A WAVE OF EVIDENCE

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

INDICATIONS

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

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

WM
- Waldenström's macroglobulinemia (WM)

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

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

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

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

BTKi=Bruton's tyrosine kinase inhibitor.

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

†Across all indications as of September 2019.

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.4 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see brief summary on the following pages.

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

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

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

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

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

Monitor complete blood counts monthly.

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	8†
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	5†
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

† Includes one event with a fatal outcome.

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies	10	2†
Vascular disorders	Hypertension	16	8

†One patient death due to histiocytic sarcoma.

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

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

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

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

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

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

Subjects with multiple events for a given adverse reaction (ADR) term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

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

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

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

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

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

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

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

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

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

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

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

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

iLLUMINATE: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

Table 9: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE

Body System Adverse Reaction§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal Disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	27	1	12	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	25	2	58	8
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and Infestations				
Pneumonia*	16	9	9	4†
Upper Respiratory Tract Infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0
Metabolism and Nutrition Disorders				
Hyperuricemia	13	1	0	0
Cardiac Disorders				
Atrial Fibrillation	12	5	0	0
General Disorders and Administration Site Conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

§ The data are not an adequate basis for comparison of ADR rates between treatment arms.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes one event with a fatal outcome.

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes 2 events with a fatal outcome.

IMBRUVICA® (ibrutinib)

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

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

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

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

Diarrhea: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

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

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

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

DRUG INTERACTIONS

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

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information].*

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Cardiac Arrhythmias:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions].*
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION .
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions].*

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SPECIAL ISSUE /ASH Meeting Recap
JANUARY 2020
VOLUME 26, ISSUE 1

COVER IMAGE © AMERICAN SOCIETY OF HEMATOLOGY / MODIFIED BY JULIANNE COSTELLO; PHOTOS © AMERICAN SOCIETY OF HEMATOLOGY

At left, Stephen J. Schuster, MD, director of the Lymphoma Program and professor at Perelman School of Medicine, Abramson Cancer Center, Penn Medicine, presents results on the bispecific antibody mosunetuzumab during a press briefing at the 61st American Society of Hematology Annual Meeting and Exposition.

INSIDE THE ISSUE

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The American Journal of Managed Care® ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512.

The 61st American Society of Hematology Annual Meeting & Exposition drew record attendance of 30,024 to Orlando, Florida, for the meeting held December 7-10, 2019.

CONTINUED FROM SP9

FROM THE CHAIRMAN

CAR T-Cell Innovation Could Improve Access, Lower Cost

FOR SOME, CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapy has been like nothing short of a miracle. Seven years ago, Emily Whitehead's lungs were failing from acute lymphoblastic leukemia and doctors told her she might never recover. She became the first child to successfully complete CAR T-cell treatment; in June 2019, the 14-year-old celebrated her journey by running a 5-kilometer road race and raising $5000 for pediatric cancer research.[1]

But the flip side of the Emily Whiteheads are those who cannot access treatment because they live too far from an academic medical center. Hometown cancer clinics cannot take on the risk of complex processes that can cost $1 million if there are significant adverse effects. This year, at the 61st American Society Hematology (ASH) Annual Meeting and Exposition in Orlando, Florida, it is clear that the next generation of treatments will erase many of these deficits. CAR T-cell treatments, or their successors, will become not just novelties for a few but the standard of care for many.

In this issue, we learn that the spirit of innovation and entrepreneurship that drives cancer drug development is alive and well. In this issue, you will read about approaches from Fate Therapeutics, bluebird bio, and Servier, whose treatment would be brought to US markets by Allogene Therapeutics. Fate's Bob Valamehr, PhD, took the bold step of using his press briefing to state that his company's early-phase investigational product costs $2500 per treatment—a head-turner in an era of 6-figure technologies.

The rise of allogenic, or "off-the-shelf" CAR T therapies will make obsolete the idea of waiting 3 weeks for a custom infusion, while addressing the challenge of graft-vs-host disease. Of course, there's much more happening in the treatment of blood cancers. But there's a new buzzword: "bispecific antibodies." Some believe therapies that target 2 antigens at once could overtake CAR T-cell treatments in importance. Notably, the presentation on one such therapy, mosenutuzumab, came from Stephen J. Schuster, MD, of Abrabamson Cancer Center at the University of Pennsylvania, who led the JULIET trial that brought forth tisagenlecleucel (Kymriah), the first CAR T-cell therapy.

More than ever, researchers are exploring how to arrest progression early on, such as the use of ibrutinib in combinations to treat chronic lymphocytic leukemia. Interest is growing in non-chemotherapy treatments, as discussed by Michael Wang, MD, of The University of Texas MD Anderson Cancer Center.

All this could make the next-generation of therapies more accessible and less costly to payers—particularly Medicare, which has struggled with CAR T-cell reimbursement. And, as we learned at ASH, that could mean a longer life with more time out of the hospital. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND FOUNDER

REFERENCE

Triola P. 14-year-old cancer survivor runs first 5K to bring her life-saving treatment to other kids. *Runner's World* website. runnersworld.com/runners-stories/a28102585/emily-whitehead-5k/. Published June 24, 2019. Accessed December 12, 2019.

Next Wave for CAR T-Cell Therapy Brings Off-the-Shelf, Multiple Myeloma Therapies

Mary Caffrey

WHEN IT COMES TO chimeric antigen receptor (CAR) T-cell therapy, the waiting may be the hardest part regarding this revolutionary, lifesaving treatment for certain leukemias and lymphomas. Manufacturing personalized treatments from a patient's own cells can take up to 3 weeks, and payer approval can add more time. The process itself is complicated and costly—at least $373,000 before administration costs—and reimbursement has sometimes been slow.[1]

That's why results highlighted December 7, 2019, at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition in Orlando, Florida, focused on the next wave of innovation, which features allogeneic, or "off-the-shelf," treatments that could offer greater convenience and lower costs—and make treatment available to more patients.

Gary Schiller, MD, of University of California, Los Angeles, Health, who moderated a press briefing on several abstracts presented at the meeting, said that advances in CAR T-cell therapy are overcoming multiple barriers:

- Although first-generation therapies primarily target the protein CD19, the next wave of treatment will attack multiple targets.
- Therapies in the pipeline will treat more blood cancers, including multiple myeloma.
- A uniform product will replace the complex manufacturing process.

"When we approach unmet needs in medicine, we solve one and we create another," said Stephen J. Schuster, MD, of Penn Medicine's Abramson Cancer Center in Philadelphia, Pennsylvania, who presented results on a novel therapy, mosunetuzumab. CAR T-cell therapy, Schuster said, has been a major advance—he led the JULIET trial in refractory B-cell lymphomas that resulted in approval of the first therapy, Novartis' tisagenlecleucel (Kymriah).[2] "However, the two-thirds of patients that don't respond to CAR T-cell therapy are now our new unmet need," he said.

Because patients eligible for CAR T are already quite ill, about a third of those enrolled in clinical trials never make it to the point of getting therapy, ASH Secretary Robert A. Brodsky, MD, director of the Division of Hematology at Johns Hopkins School of Medicine, said during a preview of the meeting.

Cost also poses a significant barrier to treatment.[1,3] Academic medical centers and Medicare have been locked in a struggle over how to pay for CAR T-cell therapy, because traditional reimbursement designs were not created with this expensive, 1-time treatment in mind.[4] Although CMS announced in August that 2020 would bring a modest increase in the new technology add-on payment, a November commentary in the *Journal of Clinical Oncology* pronounced that "this quick fix does not go far enough."[5] The authors estimated that hospitals lose $300,000 for every patient treated with this technology.

Schuster presented results from a dosing study involving mosunetuzumab, a bispecific antibody tested in 270 patients with B-cell lymphomas that had returned or not responded to at least 3 therapies, including some patients who relapsed or failed to respond to CAR T-cell therapy.[6] The group included 30 patients previously treated with CAR T-cell therapy. In a press preview ahead of the 2019 meeting, ASH leaders speculated that bispecific antibodies could supplant first-generation CAR T-cell treatments in some cancers if they can treat patients quickly at a lower cost.

Unlike CAR T-cell therapy, mosunetuzumab does not require individualized genetic modification of a patient's T cells. Instead, this therapy redirects T cells to engage and eliminate B cells, Schuster said. The new therapy produced durable responses in 37% of the patients with aggressive non-Hodgkin lymphoma (NHL), a group that would benefit most from not having to wait for individualized manufactured cells. Higher exposure to mosunetuzumab brought better responses, and a higher-dose study is now enrolling patients, Schuster said.

Across the studies presented at the meeting, patients generally experienced lower grades of cytokine release syndrome (CRS) than seen in the first generation of CAR T-cell therapy. Hospitalization due to CRS has been a significant contributor to cost in the first generation of CAR T-cell therapy; estimates of managing severe cases range from $56,000 to more than $200,000.[7]

However, Schiller said, ease of access will likely be the top selling point of these new therapies in the coming years. "An off-the-shelf product is attractive because of feasibility issues," Schiller said. For patients previously treated with CAR T-cell therapy, it appears this new wave of treatments may salvage responses after a relapse, he said: "It all depends on durability.

"[For a] simple clinician…who needs to take care of patients with desperate diseases, tolerability is secondary to access and feasibility," Schiller continued. "So whatever product—be it cellular or bifunctional—that we have access to tomorrow will be better and easier for us to use."

Abstracts presented at the briefing highlighted what's in the pipeline:

MOSUNETUZUMAB. Schuster reported on complete remission (CR) in patients with relapsed/refractory NHL who were treated with the study drug. In this phase 1/1b open-label study, according to the abstract, mosunetuzumab is given with step-up dosing on days 1, 8, and 15 of cycle 1, then as a fixed-dose on day 1 of each subsequent 21-day cycle, for a maximum of 17 cycles. Outcomes are best objective response rate (ORR), maximum tolerated dose (MTD), and tolerability.[6]

Results were the following:

- The treatment produced promising responses in patients with aggressive NHL. Among 124 patients (diffuse large B-cell lymphoma, follicular lymphoma), ORR was 37.1% (46 patients) and CR was 19.4% (24 patients) (**FIGURE**).
- As expected, responses were better for patients with indolent NHL. Among the 67 patients, ORR was 62.7% (42 patients), and 29 (43.3%) had a CR.
- Among the first 18 patients with prior CAR T-cell therapy, ORR was 38.9% (7 patients), and 4 patients (22.2%) had a CR.
- Four patients were able to be retreated with mosunetuzumab; among these, 3 (75%) had an ORR, and 1 had a CR.

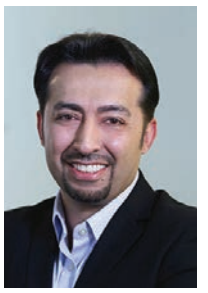
"I have stopped therapy in some patients after 6 months, and they have remained in remission," Schuster said. "Some patients have remained in remission without additional therapy for more than a year." »

SCHILLER

Gary Schiller, MD, director, Bone Marrow/Stem Cell Transplantation, David Geffen School of Medicine, University of California, Los Angeles

SCHUSTER

Stephen J. Schuster, MD, professor, Perelman School of Medicine; Abramson Cancer Center, Penn Medicine, Philadelphia, Pennsylvania



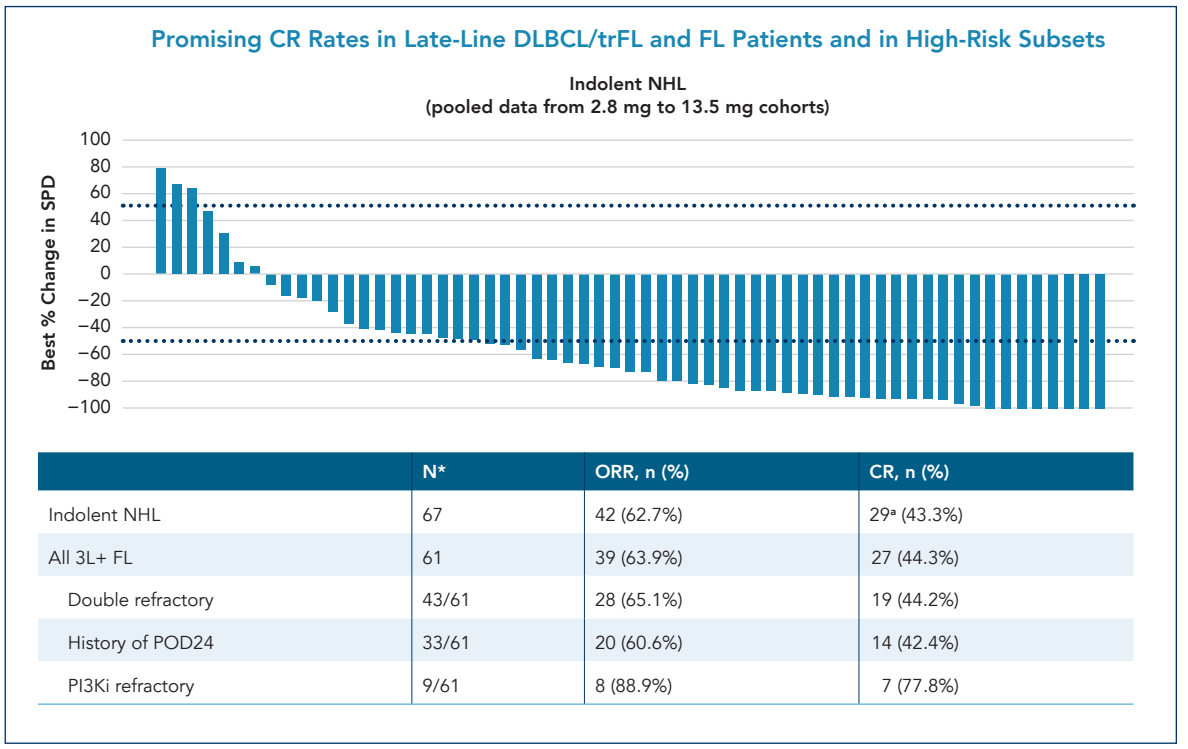
VALAMEHR

Bob Valamehr, PhD, chief development officer, Fate Therapeutics

MADDURI

Deepu Madduri, MD, assistant professor of medicine, hematology and oncology, Mount Sinai, New York City

FIGURE. Durable CR in Aggressive and Indolent NHL



	N*	ORR, n (%)	CR, n (%)
Indolent NHL	67	42 (62.7%)	29[a] (43.3%)
All 3L+ FL	61	39 (63.9%)	27 (44.3%)
Double refractory	43/61	28 (65.1%)	19 (44.2%)
History of POD24	33/61	20 (60.6%)	14 (42.4%)
PI3Ki refractory	9/61	8 (88.9%)	7 (77.8%)

CR indicates complete response, DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease within 24 months from start of first-line therapy; SCT, stem cell transplant; SPD, sum of product diameters; trFL, transformed follicular lymphoma

[a]24/29 patients remain in CR (up to 26 months off initial treatment)

Presented by Stephen J. Schuster, MD, at the 61st American Society of Hematology Annual Meeting and Exposition; Orlando, FL; December 7, 2019.

CAR NK PROOF-OF-CONCEPT. Bob Valamehr, PhD, of Fate Therapeutics, presented proof-of-concept data on an off-the-shelf cellular immunotherapy that targets 2 proteins on the surface of lymphoma cells.[8] The treatment, a targeted CAR natural killer (NK) cell, would be enhanced with features to take advantage of the properties of NK cells—their ability to attack and kill many types of cells—while extending the cells' durability. "NK cells are multifaceted and can be viewed as a jack-of-all-trades when it comes to protecting the host, whereas T cells can act in only 1 way," Valamehr said.

Fate Therapeutics developed a master line of NK cells induced from specialized stem cells (iNK cells), known as FT596, which overcomes a challenge of CAR T therapy: lack of uniformity that can occur with individualized products. "When you [manufacture] the product, not every cell is engineered, and not every engineered cell is pristine," Valamehr said.

According to the abstract,[8] FT596 cells are designed to carry 3 genes at once:

- An NK cell-calibrated CAR that targets CD19
- Noncleavable CD16, which enhances binding activity
- A recombinant fusion of interleukin (IL) 15 and IL-15 receptor-α (IL-Rα) that extends persistence of the cells

Investigators did experiments in both in vitro and in mouse models and found that iNK cells engineered with both CD19-CAR and IL-Rα "were curative against B-cell lymphoma" compared with iNK cells either alone or modified only with CD19-CAR. The investigators next performed tests using various combinations with rituximab and reported that "only FT596 was able to effectively eliminate the CD19 antigen escaped target cell."[7]

According to the abstract, experiments using the allogeneic therapy on a mouse model showed that FT596 "demonstrated improved survival and safety over primary CAR19 T cells," whether used as alone or in combination with rituximab. Experiments with rituximab showed great potential for that combination.

If successful, this approach could be administered much like traditional therapies, according to Valamehr. The process creates "a homogeneous, high-quality product that's low cost," he said. "Each dose is $2500. It's directly infused; there is no processing needed, so it becomes a true, administered off-the-shelf product in an outpatient setting."

MULTIPLE MYELOMA. The session also covered a pair of CAR T-cell therapies for multiple myeloma, taking advantage of the dual target approach. Results from CARTITUDE-1,[9] funded by Janssen, confirm results from the LEGEND-2 study[10] for a therapy containing 2 proteins designed to target the B-cell maturation antigen. Deepu Madduri, MD, of Mount Sinai in New York, New York, shared the news that the FDA granted JNJ-4528 breakthrough therapy designation on the eve of the ASH meeting—December 6, 2019.[11]

"We know that there have been a lot of advances over the last few years [in] multiple myeloma," Madduri said, "and so people are living longer." However, for patients who have failed all available therapies, "median overall survival is less than 12 months," he said.

This study involved 29 patients, 25 of whom had at least 3 prior therapies, including autologous transplantation. The investigators said the results show that JNJ-4528 at a dose of 0.75 x 10^6 CAR-positive cells/kg brings an early and deep response, featuring minimal residual disease negativity "in all evaluable patients tested."[9]

Of note:

- Not only were CRS events of lower grade than in first-generation CAR T therapies, but the median time of onset was 7 days, >90% between 5 and 9 days, later than in the past.
- Neurotoxicity was infrequently observed and generally low grade.
- Early and deep responses were seen: 100% ORR, with ≥CR 69% at 6 months.
- The median time to first response was 1 month, as was the median time to ≥CR; 27 of 29 patients were progression free at 6 months. ◆

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Update on UCART19 Arrives Amid News on Allogeneic CAR T Therapy

Mary Caffrey

DESPITE ALL THE BUZZ about allogeneic or "off-the-shelf" chimeric antigen receptor (CAR) T-cell therapy at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition in Orlando, Florida, the concept was not new to ASH meetings.

At the 2018 gathering in San Diego, California, the French biotech Servier presented data on its universal anti-CD19 therapy, UCART19.[1] The product made news amid reports that in pooled data from a pair of ongoing phase 1 studies (1 with adults, 1 with pediatric patients), 82% of patients who received a novel lymphodepletion regimen had achieved remission.[2] This is done by knocking out the *CD52* gene, allowing the therapy alemtuzumab to be used in this process.

UCART19 is manufactured from healthy donor T cells and features a safety switch, the CD20 mimotope RQR8, that lets rituximab bind to the CAR T cells. This halts the runaway responses associated with CAR T treatment, dramatically reducing adverse events such as cytokine response syndrome. This mechanism was initially developed by Servier's collaborator, Cellectis, which exclusively licensed UCART19 to Servier.[3] Because the product is created from donor cells, the therapy features technology to deal with graft-vs-host disease—notably, a T-cell receptor (TCR) knockout that disrupts the *TRAC* gene.

Results reported at the 2019 ASH meeting show that healthy donor CAR T cells (n = 11) expanded significantly during the manufacturing process compared with those derived from B-cell acute lymphoblastic leukemia (B-ALL; n = 9), chronic lymphocytic leukemia (CLL; n = 8), or diffuse large B-cell lymphoma (DLBCL; n = 8).[4] Investigators said in their abstract that median CAR expression level was higher for patients with CLL using the CAR T-cell product compared with B-ALL patients and healthy donors. The TCR knockout led to the following results:

- CD3 expression was lost on healthy donor TCR-negative CAR T cells, except for a distinct population called γδ CAR T cells.
- CLL and DLBCL CD8-CAR cells expressed higher levels of PD-1 than healthy donor CD8- CAR T cells.
- In 2018, CAR-CD8-CD27-PD-1 T cells were described as "functionally important" and correlated with clinical outcomes in patients who got the CLL CAR T cells.
- Healthy donor and healthy donor TCR CAR T cells had more CD8, CD27, and PD-1 CAR T cells compared with those derived from CLL and DLBCL but similar to the amount of those in patients with B-ALL.

Evidence-Based Oncology™ (*EBO*) posed questions about UCART19 to Patrick Therasse, MD, PhD, head of Research & Development, Oncology, at Servier Group. Under a licensing agreement with Pfizer, if successfully developed and then approved by the FDA, the product would be marketed in the United States through Allogene Therapeutics. Pfizer bought a 25% stake in Allogene in 2018.

EBO: The approach of UCART19 appears to strike a balance: You use healthier cells to overcome weaknesses that develop due to prior treatments and cancer itself, while guarding against the potential for rejection through modification, via knockouts of *TRAC* and *CD52*. Is this the basic concept? What are the advantages and disadvantages compared with the current approach to CAR T-cell treatment?

THERASSE: Yes, this is basically the approach: overcoming the limitations associated with the use of autologous CAR T approaches including lengthy vein-to-vein time, manufacturing failure, variable potency, and high production cost. We believe that the use of innovative technology to modify nonmatched allogeneic healthy donor T cells may allow the treatment of a broad patient population with a product of consistent quality standards. If UCART19 is approved, the treatment could begin soon after diagnosis, which could be vital in a fast-progressing disease such as acute lymphoblastic leukemia [ALL].

EBO: UCART19 uses trademarked technology called TALEN. What does TALEN stand for, and can you discuss the basic mechanism?

THERASSE: TALEN is a gene-editing technology pioneered and owned by our partner Cellectis. It stands for "transcription activator-like effector nuclease." TALEN products are designed by fusing the DNA cutting domain of a nuclease to TALE domains, which can be tailored to specifically recognize a unique DNA sequence. These fusion proteins serve as readily targetable "DNA scissors" for gene-editing applications that enable us to perform targeted genome modifications such as sequence insertion, deletion, repair, and replacement in living cells.

EBO: How does UCART19 stand apart from other allogeneic treatments presented at the 2019 meeting?

THERASSE: UCART19 is the most advanced allogeneic CAR T product in clinical development. It entered clinical development in 2016, and encouraging clinical data from the first 21 patients were presented during ASH [in 2018].[1] Today, 3 clinical trials are ongoing in pediatric and adult ALL and non-Hodgkin lymphoma.

EBO: Will this approach be less costly than current CAR T-cell treatments—not just in the therapy itself but also in administrative/hospitalization costs? Have estimates been developed? If so, what are the potential benefits to payers, especially Medicare?

THERASSE: Cost is clearly a key parameter with regard to CAR Ts. By using the allogeneic approach, we hope to be able to treat 10 to 100 patients from a single manufacturing run. This will certainly allow to decrease the cost of treatment compared with the autologous approach.

EBO: There have already been discussions that CAR T-cell therapy should be given earlier, before cells are depleted by prior treatments. Is there potential for allogeneic treatments to jump ahead of the current CAR-T offerings in the treatment guidelines?

THERASSE: Using CAR-T cell therapy earlier in the management of ALL patients has been discussed. One of the benefits could be to avoid the long-term toxicity that may be associated with the use of chemotherapies, especially in pediatric patients. It is too early to tell if allogeneic CAR Ts would behave differently than autologous CAR Ts in that setting. »

THERASSE
Patrick Therasse, MD, PhD, head of Research & Development, Oncology, Servier Group

EBO: Is it possible yet to say what the difference would be in toxicity compared with current CAR T treatments?

THERASSE: Improving the toxicity profile of CAR T-cell therapies is also one of our objectives when developing next-generation allogeneic CAR Ts. It is too early today to make any conclusion, but preliminary data suggest that toxicity may differ between autologous and allogeneic CAR T-cells.

EBO: What are the next research steps?

THERASSE: Improving the efficacy while preserving the toxicity profile of CAR Ts, together with optimizing the manufacturing process, are our main objectives today. For the future, challenges will be to extend CAR T-cell therapies to other targets and indications, including solid tumors. ◆

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Persistence of CAR T Cells Seen in "Next-Generation" Anti-BCMA Therapy, bluebird bio's Ide-cel

Mary Caffrey

NICULESCU

Liviu Niculescu, MD, PhD, senior vice president, global medical affairs, bluebird bio

ALTHOUGH RESULTS FOR JANSSEN'S investigational chimeric antigen receptor (CAR) T-cell therapy directed against B-cell maturation antigen (BCMA) appeared on the press program at the 61st American Society of Hematology (ASH) in Orlando, Florida,[1] analysts were equally impressed[2] with results for a competing anti-BCMA from bluebird bio and Bristol-Myers Squibb.[3]

The company presented updated phase 1 results[3] for a revamped version of bb2121 that point to sustained responses for patients with relapsed/refractory multiple myeloma (RRMM). Both versions are built on the idecabtagene vicleucel (ide-cel; bb2121). Separately, bluebird bio and Bristol-Myers Squibb also announced positive topline results for a phase 2 pivotal trial called KarMMa.[4]

The updated phase 1 dose escalation trial (CRB-402) is a first-in-human study of bb21217, so called because ide-cel is enhanced with the phosphoinositide 3-kinase inhibitor bb007 to create "memory-like" T cells. As of September 4, 2019, the study included data for 38 patients with a median of 6 prior lines of therapy; 82% had at least 1 autologous stem cell transplant:

- 24 patients received the therapy at 3 dose levels: 12 at 150 x 10^6 CAR+ T cells; 6 at 300 x 10^6 CAR+ T cells; and 6 at 450 x 10^6 CAR+ T cells.
- 14 patients received therapy in the dose expansion cohort at 2 dose levels: 8 at 300 x 10^6 CAR+ T cells and 6 at 450 x 10^6 CAR+ T cells.

Evidence-Based Oncology™ (*EBO*) discussed the results and CAR T-cell therapy for multiple myeloma with bluebird bio's Liviu Niculescu, MD, PhD, senior vice president for global medical affairs.

EBO: We've been hearing about CAR T-cell therapy in multiple myeloma for a while. What are the challenges of using a CAR T-cell approach for this particular blood cancer?

NICULESCU: The fundamental challenge associated with the treatment of multiple myeloma is the relentlessness of the disease. Treatment outcomes have decidedly improved for myeloma patients over the last decade, which is reflective of the introduction and availability of many new effective treatment options. However, the disease remains incurable with the majority of patients experiencing relapse, at which time the patient's disease becomes more and more difficult to treat.

CAR T therapies are shown to provide relapsed and refractory myeloma patients with durable remissions after a single administration, allowing these patients additional time to live without their disease getting worse. However, many of these patients relapse and require further treatment. Understanding the underlying mechanism of relapse after CAR T therapy is a key challenge today. When we begin to understand this incredibly complex question, we can further explore ways to improve CAR T therapies. This question of how to improve CAR T therapy in order to increase outcomes for patients is what led to the development of bb21217.

These therapies are promising and at the forefront of innovative science, but there are also practical challenges. Many patients with multiple myeloma are treated in community practice settings and CAR T therapy is only administered in specialized centers. So, finding the right treatment centers and providing a smooth experience for the patient is a key focus as we potentially bring CAR T therapy to patients with multiple myeloma.

EBO: BCMA-based immunotherapies for multiple myeloma have received lots of attention. Can you discuss the value of this approach [bb21217] generally and how bluebird bio's concept of enriching T cells to improve "memory" improves persistence?

NICULESCU: bb21217 is an investigational BCMA-targeted CAR T-cell therapy that uses the idecabtagene vicleucel (ide-cel; bb2121) CAR molecule and is cultured with the PI3 kinase inhibitor (bb007) to enrich for T cells displaying a memory-like phenotype

with the intention to increase the *in vivo* persistence of CAR T cells. Evidence suggests that memory like T cells may persist in patients for a longer time than other types of T cells, and it is hypothesized that the persistent memory like CAR T cells may be important for increasing durability of response.

"As we continue to gain more experience with CAR T therapies and conduct additional research, physicians have become more comfortable with managing common adverse events like cytokine release syndrome and neurotoxicity."

—Liviu Niculescu, MD,
senior vice president , Global Medical Affairs
bluebird bio

As of September 4, 2019, CAR T-cell persistence in CRB-402 was observed in 8 of 10 patients with ongoing response and evaluable at six months, and 2 out of 2 patients with ongoing response and evaluable at 18 months. Initial data, based on limited follow-up, suggest that enrichment for memory-like CAR T cells in bb21217 drug product was associated with both increased peak CAR T expansion and achievement of sustained clinical response at 6 months.

Longer follow-up is needed to define any association with long-term persistence and response. It is important to note that these are early data and analyses of long-term CAR T-cell persistence require additional follow-up. We continue to assess the functional persistence of bb21217 in this ongoing study, as well as its potential correlation with durability of response.

EBO: Toxicity has been an issue with the first generation of CAR T-cell therapy, although this seems to be improving with the next generation of treatments. How does bb21217 compare in toxicity relative to both the first generation of CAR T and some of the newer treatments on the horizon?

NICULESCU: As of September 4, 2019, the safety profile of bb21217 is consistent with known toxicities of CAR T therapies, regardless of dose level. As we continue gain more experience with CAR T therapies and conduct additional research, physicians have become more comfortable with managing common adverse events (AE) like cytokine release syndrome and neurotoxicity. AE management guidelines have been developed and we can see improvements in the prevention and treatment of these AEs.

EBO: Can you discuss the effectiveness of bb21217 in helping patients achieve undetectable minimal residual disease (MRD)?

NICULESCU: As of September 4, 2019, evidence of myeloma in the bone marrow, known as minimal residual disease (MRD), was undetectable by next-generation sequencing at a sensitivity level of 10^{-5} in 94% (n=16/17) of all confirmed responders who had evaluable bone marrow samples (patients with ≥ PR and ≥ 1 valid post-baseline MRD assessment).

EBO: As multiple myeloma is a very heterogeneous disease, which patients would benefit most from bb21217?

NICULESCU: We are investigating bb21217 in a group of heavily pretreated multiple myeloma patients who have been exposed to most mechanisms of action currently available to treat the disease (anti-CD38, proteasome inhibitors and immunomodulators). These patients are now refractory to their treatment, meaning that their disease is progressing during treatment, or within 60 days after, so they have very limited additional options.

We can't comment on the market use of an investigational therapy, but it is important to note that multiple myeloma is a relentless disease and there is significant need to find new treatment options for patients who advance through the current therapies available to them.

The current data support ongoing investigation to fully understand the potential role of bb21217 in the multiple myeloma treatment paradigm. We continue to enroll patients at the recommended phase 2 dose in order to further evaluate the efficacy of bb21217 and we look forward to sharing updated data as it matures. ◆

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CLINICAL FINDINGS

Three-Quarters of Patients on Ibrutinib-Venetoclax Combo in CLL Achieve Undetectable MRD in CAPTIVATE

Mary Caffrey

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WILDGUST
Mark Wildgust, PhD, vice president, Global Medical Affairs, Oncology, Janssen

MOST PATIENTS WITH PREVIOUSLY untreated chronic lymphocytic leukemia (CLL) who received a combination of ibrutinib and venetoclax achieved undetectable minimal residual disease (MRD), according to partial results from the phase 2 CAPTIVATE trial[1] presented on December 7, 2019, at the 61st American Society of Hematology (ASH) Annual Meeting and Exposition in Orlando, Florida.

Patients in the study, who were under age 70, received a daily oral dose of 420 mg of ibrutinib (Imbruvica, Janssen) for 3 cycles (28 days each), followed by 12 cycles of ibrutinib with an escalating dose of venetoclax (Venclexta/Venclyxto) up to 400 mg. Of the evaluable patients, 75% achieved undetectable MRD in their peripheral blood at some point after baseline, whereas 72% achieved undetectable MRD in their bone marrow.

Lead investigator Constantine Tam, MD, of the Peter MacCallum Cancer Centre, Victoria, Australia, presented results from the MRD cohort prior to randomization based on their MRD status. Results presented at ASH involved 164 patients who began the trial and 151 who were able to complete all 12 cycles. In the next phase of the trial, to be reported later, patients with undetectable MRD were randomized 1:1 to receive ibrutinib or placebo, whereas those with detectable MRD will be randomized to receive ibrutinib or ibrutinib with venetoclax.

Based on the successful results to date, Tam added, "We have now accrued a third [group of] 159 patients in a separate, fixed-duration cohort," and these patients will receive the combination therapy "without any further treatment."

Ibrutinib has transformed CLL care as the only daily inhibitor of Bruton tyrosine kinase.[2] Its benefits have been seen in patients with first-line CLL in both the RESONATE-2[3] and ECOG-1912[4] trials; investigators for these studies reported additional data during ASH 2019. Venetoclax is an oral inhibitor of BCL2, proteins that regulate cell death, or apoptosis. As CAPTIVATE investigators discussed in their abstract, the 2 therapies are believed to have synergistic properties, given the ability of ibrutinib to draw CLL cells from lymphoid tissue into the blood, where they would rely on BCL2.[1] Tam is also leading studies of the 2-drug combination in mantle cell lymphoma.

MRD is an increasingly important measure of the small number of cancer cells remaining in the body after treatment. These cells can be hard to detect, but they are important because they can be indicators of which patients will relapse. The use of MRD as a guide for treatment will be the focus of CAPTIVATE when the next results are reported, and this will help answer one of the important questions the trial is designed to address, Mark Wildgust, PhD, vice president, Global Medical Affairs, Oncology, Janssen, said in an interview with *Evidence-Based Oncology*™.

Before ibrutinib, he said, the reason patients with CLL would only be treated with 6 cycles of the regimen known as FCR—fludarabine, cyclophosphamide, and rituximab—was because they could not tolerate any more therapy. Ibrutinib "changed the paradigm," Wildgust said; he noted that new data from ECOG-1912 presented at ASH show that continuously treating patients with ibrutinib is better than the old "gold standard" of 6 cycles of FCR.[5]

With CAPTIVATE, the question of stopping therapy is raised not because patients can no longer tolerate treatment, but because once they are MRD negative, it might be possible to stop therapy without CLL progressing. Thus, he said, the study seeks to answer (1) Can patients who have 15 cycles of therapy reach a point where MRD cannot be measured, and (2) If therapy is stopped, is it safe?

Clinicians were afforded an early glimpse at CAPTIVATE data in June 2018 during the annual meeting of the American Society of Clinical Oncology, where 77% of the first 30 patients had undetectable MRD after 6 cycles of the combination treatment.[6] Presenters explained at that time the lead-in with ibrutinib alone helps prevent tumor lysis syndrome; this protocol is also seen in the CLARITY trial for patients with relapsed or refractory CLL.[7]

In the results presented at ASH 2019, the median treatment duration was 14.7 months (range, 0.5-19.9 months) with ibrutinib and 12 months (range, 0.8-12.7 months) with venetoclax.[1] The most common adverse events (AEs) of any grade were diarrhea (31%) with single-agent ibrutinib and diarrhea (60%), neutropenia (40%), and nausea (34%) with the combination. AEs leading to dose reductions occurred in 20% of patients, and AEs that caused patients to stop therapy occurred in 7% of patients (ibrutinib 5%, venetoclax, 4%).

"We are encouraged by these data and the potentially potent combination of ibrutinib plus venetoclax."

—Constantine Tam, MD, Peter MacCallum Cancer Centre, Victoria, Australia

"This study was not intended to enroll high-risk patients," Tam said during his presentation, but many in the original 164 enrollees (median age, 58 years) had genetic risk factors:

- 16% had deletion 17p.
- 20% had deletion 17p or *TP53* mutation.
- 16% had deletion 11q without deletion 17p.
- 19% had complex karyotype.
- 59% had unmutated immunoglobin heavy chain gene mutation.

Tam noted the high rate of undetectable MRD was seen across subgroups, including these high-risk patients: deletion 17p, 75%; deletion 17p or TP53 mutation, 70%; deletion 11q, 84%; complex karyotype, 83%; and unmutated immunoglobin heavy chain gene mutation, 81%.

Of the patients who reached the combination therapy cycles:

- Undetectable MRD in peripheral blood rose over time, from 57% after 6 cycles to 68% after 9 cycles, and 73% after 12 cycles
- Undetectable MRD was achieved in 75% of patients (122 of 163) in peripheral blood when measured and 72% (111 of 155 patients) in bone marrow

"We are encouraged by these data and the potentially potent combination of ibrutinib plus venetoclax treatment for CLL and potentially other blood cancers in the future," Tam said in a statement.

NEW ANALYSIS FROM EARLIER STUDIES. An integrated analysis[8] of the RESONATE and RESONATE-2 studies, which includes up to 6 years of follow-up, covered a total of 271 patients, including 136 patients who received ibrutinib as first-line therapy and 135 who received it for relapsed or refractory CLL. The analysis shows that using ibrutinib earlier in the treatment of CLL results in better progression-free survival, overall survival, and overall riskreduction. Results include the following:

- A higher share of patients treated with ibrutinib in earlier lines remained progression-free or alive at 60 months (first line, 70%; 1-2 lines prior, 60%; 3 or more, 33%).
- First-line treatment brought a 34% reduction in risk of disease progression or death compared with 1 to 2 prior lines, with a hazard ratio (HR) of 0.66 (95% CI, 0.40-1.09).
- Progression-free survival was prolonged for first-line treatment versus 3 or more lines, with an HR of 0.32 (95% CI, 0.21-0.49) and 1 to 2 lines versus 3 or more lines, with an HR of 0.48 (95% CI, 0.30-0.77).

Wildgust said Janssen will continue to support research to explore questions of whether patients can safely stop therapy for CLL, and if so, what is the best way.

"We're at a point where ibrutinib has 5 front-line studies that show a survival benefit," he said, including the new RESONATE analyses that show earlier treatment is better. "Now the question is whether we can look at potential ways of stopping—and as a company, we're looking at all those different ways of stopping." ◆

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Adding Daratumumab to Carfilzomib, Dexamethasone Improves PFS in Relapsed/Refractory Multiple Myeloma

Mary Caffrey

USING THE MONOCLONAL ANTIBODY daratumumab with carfilzomib and dexamethasone boosts survival benefits for patients with relapsed or refractory multiple myeloma (RRMM), including those who have taken lenalidomide, according to findings from CANDOR,[1] a phase 3 study presented on December 10, 2019, at the 61st American Society of Hematology Annual Meeting and Exposition in Orlando, Florida.

The triple-therapy combination led to a 37% reduction in the risk of disease progression or death compared with those taking carfilzomib and dexamethasone alone. Carfilzomib, a selective proteasome inhibitor, is sold as Kyprolis by Amgen; a once-weekly combination with dexamethasone was approved for patients with RRMM in October 2018.[2] Amgen funded the CANDOR trial.

Although survival rates for multiple myeloma have improved as treatment options have increased, the disease remains incurable, and some patients must stop current agents such as lenalidomide or bortezomib due to toxicity.[3,4] Thus, finding new therapies or combinations is a priority, according to Saad Z. Usmani, MD, of Atrium Health, lead author of the CANDOR study.

"The majority of patients have disease progression on lenalidomide, and of the 6 treatment combinations that are currently approved in this setting, 4 have lenalidomide as part of their treatment combination," Usmani said in a statement.[5] "It makes little sense to rechallenge a patient with something they are progressing on just by adding other drugs. So, there is a need for novel therapeutic options for patients with multiple myeloma who have relapsed or are refractory to lenalidomide-based treatments."

CANDOR is a phase 3, open-label trial in which 466 patients treated with 1 to 3 prior therapies were randomized 2:1 to receive the triple combination (KdD) or carfilzomib and dexamethasone (Kd).[1] In an earlier phase I study, investigators found that adding daratumumab improves survival in patients with RRMM.[6] Daratumumab (Darxalex, Janssen) targets CD38, causing cell death.

Results of the trial showed the following:

- After a median follow-up of 17 months, the median progression-free survival (PFS) had not been reached for KdD, whereas median PFS was 15.8 months for Kd; the hazard ratio (HR) was 0.63 (95% CI, 0.46-0.85; $P = .0014$).
- At this point, Usmani said there are no differences in overall survival.
- The patients receiving triple therapy had a better overall response rate, or 84.3% compared with 74.7% for Kd.
- Complete response rates were 28.5% for KdD versus 10.4% for Kd.
- Rates of undetectable minimal residual disease at 12 months were 12.5% for KdD versus 1.3%.
- Patients on triple therapy were in treatment for 70.1 weeks, compared with 40.3 weeks for the Kd group.

Patients in the CANDOR trial had a median age of 64 years; 42.3% previously had lenalidomide therapies, and 90.3% »

USMANI
Saad Z. Usmani, MD, Atrium Health

underwent regimens with bortezomib. In a press briefing, Usmani pointed out results for those previously treated with lenalidomide. "This is perhaps one of the more important subgroups," he said.

In patients with prior lenalidomide exposure, the median PFS was not reached in the triple- therapy group, whereas it was 12.1 months for the Kd group (HR, 0.52; 95% CI, 0.34-80). Among patients who were lenalidomide refractory, the median PFS for the triple-therapy group was not reached; it was 11.1 months for the Kd group (HR, 0.45; 95% CI, 0.28-74).

"So, the PFS benefit was maintained not just in other subgroups, but in these 2 clinically meaningful subgroups as well," Usmani said.

Patients in the triple-therapy group had higher rates of serious adverse events, including 5 treatment-related deaths due to pneumonia, sepsis, septic shock infection, and cardiac arrest. The most common adverse events were thrombocytopenia, anemia, diarrhea, hypertension, upper respiratory tract infection, fatigue, and shortness of breath. Investigators reported cardiac events in 5% to 8% of patients, consistent with prior studies, but heart failure was lower in the triple-therapy group.[1]

In a statement, Usmani pointed out that multiple myeloma is a heterogenous disease, so multiple treatment options are needed to address different patient needs. "Even within a single patient, we see many different clones, at an average of 10 to 15 clones at the time of diagnosis—so if you want optimal disease control, you have to target different mechanisms of action to control the disease more effectively."[5] ◆

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Oral Azacitidine in AML Maintenance Boosts Overall Survival by 31%

Mary Caffrey

BRODSKY

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WEI

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OLDER PATIENTS WITH acute myeloid leukemia (AML) who achieved remission with chemotherapy saw significant improvements in both relapse-free and overall survival (OS) with Celgene's investigational oral azacitidine, CC-486, a result that investigators say finally validates the role of maintenance therapy in this disease.

Phase 3 findings from the QUAZAR trial,[1] presented on December 10, 2019, at the 61st American Society of Hematology Annual Meeting and Exposition in Orlando, Florida, showed the therapy brought OS improvements across a range of subgroups, including with or without consolidation, and those older and younger than age 65.

AML is a common form of adult leukemia and tends to strike elderly patients, with less than 30% of those who develop this cancer surviving for 5 years.[2] The 472 study patients ranged from 55 to 86 years of age (mean age, 68). Participants had to achieve a complete response (CR) or CR with incomplete recovery count after induction chemotherapy.[1] They could not be candidates for a bone marrow transplant. With 4 months of CR, patients were randomized 1:1 to receive 300 mg of CC-486 or placebo for 14 days of a 28-day cycle until relapse.

After a median follow-up of 41.2 months, investigators reported the following results[3]:

- The primary end point, OS, was 24.7 months for the study drug group versus 14.8 months for placebo, for a 31% lower risk of death; hazard ratio, 0.69 (95% CI, 0.55-0.86, $P = .0009$).
- Risk of relapse was 35% lower among those taking CC-486: 10.2 months for those on the study drug versus 4.8 months on placebo; hazard ratio, 0.65 (95% CI, 0.52-0.81, $P = .0001$).
- Patients on CC-486 were more likely to attain undetectable minimal residual disease.
- Serious adverse events (AEs) were reported for 34% of the CC-486 group and 25% of the placebo arm, with the most common AE in both groups being neutropenia or gastrointestinal events.
- Treatment discontinuation due to AEs was infrequent.
- CC-486 did not adversely affect quality of life compared with placebo.

Because AML is not considered a curable disease, investigators believe the findings offer the opportunity for prevention of progression instead of waiting for a relapse to treat the disease.

"The AML community has been trying to validate the role of maintenance therapies to extend initial treatment responses for many decades and—until now—without success," lead study author Andrew H. Wei, MBBS, PhD, of Alfred Hospital, Melbourne, Australia, said in a statement.[4] "While several agents have been studied and shown to increase relapse-free duration, demonstration of a survival benefit has been elusive."

Robert Brodsky, MD, director of the Division of Hematology at Johns Hopkins School of Medicine, said CC-486 could offer a maintenance therapy for patients with AML who really have not had a good option. For these patients, "It's pretty easy to get into remission, but it's very short-lived—there's never any consolidation that's really been effective," he said.

A viable maintenance option in treating AML could bring significant savings to the healthcare system, especially Medicare. An analysis of the cost burden of AML presented at the 2017 ASH meeting found that relapse brings frequent and costly hospitalizations; the least expensive episode from low-intensity

chemotherapy was $53,081; the one with the highest cost was a bone marrow transplant at $329,621.[5]

Brodsky and Wei both said having an oral drug for maintenance is beneficial and convenient for patients. The drug is a cytidine nucleoside analogue that contributes to hypomethylation, or modification of DNA, and cytotoxicity of hematopoietic cells in the bone marrow, leading to cell death. Renal toxicities have been reported in the intravenous version of azacitidine in the treatment for myelodysplastic syndrome, but this was among the AEs reported in the QUAZAR-AML-001 trial.

Wei said he anticipates that CC-486 will become "a fundamental building block" of more effective drug combinations in AML, perhaps with venetoclax.

When Celgene announced topline results for QUAZAR AML-001 in the fall of 2019, company officials said regulatory filings would occur in the first half of 2020.[6] Celgene, which was recently acquired by Bristol-Myers Squibb, funded the study. ◆

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Use Blinatumomab, Not Standard Chemo, for Children With Relapsed B-ALL, Study Finds

Mary Caffrey

CHILDREN WITH A FIRST RELAPSE of B-cell acute lymphoblastic leukemia (B-ALL) avoided infections and were more likely to receive a bone marrow transplant if treated with the immunotherapy blinatumomab instead of standard chemotherapy, according to a study presented on December 10, 2019, at the 61st American Society of Hematology (ASH) Annual Meeting and Exposition in Orlando, Florida.

Use of blinatumomab improved survival by 20%, and the drop in minimal residual disease (MRD) was so dramatic that an independent review panel stopped the phase 3 trial of children and young adults early, after it was clear that the drug's benefits were enough to set a new standard of care. Investigators had planned to randomize 220 patients when the study began in January 2015, but randomization was halted in September 2019 at 208 patients.[1]

Blinatumomab, marketed by Amgen as Blincyto, is approved for use in relapsed and refractory B-ALL,[2] but this trial from the Children's Oncology Group sought to confirm its benefits in pediatric patients who have still have MRD after a month of chemotherapy following a relapse. Trial participants were aged between 1 and 30 years.

Patrick A. Brown, MD, of Johns Hopkins University's Kimmel Comprehensive Cancer Center and the study's lead author, explained during a press briefing that prognosis is poor for the 15% of children and young adults with B-ALL who have a relapse within the first 3 years of diagnosis. Getting these patients to transplant offers the best chance for a cure, but this has required a 2-part chemotherapy protocol that threatens survival if infections or other complications arise during the process, which can take up to 4 months.

"This is a new standard of care," said Robert Brodsky, MD, ASH secretary and director of the Division of Hematology at Johns Hopkins, who moderated the briefing on the ASH late-breaking session. Pediatric B-ALL patients can be challenging to treat, he said, because "when they relapse, it's very hard to get them back into remission." Driving down MRD levels is essential for a bone marrow transplant to work, and the results presented on December 10 show that blinatumomab greatly improves those odds, Brodsky said.

In this study, all patients who had a relapse received the standard 1-month chemotherapy reinduction. They were stratified by risk level, based on the timing of their relapse or a measurement of MRD. Brown explained that those with early relapse, or late relapse but elevated MRD levels, proceeded to the consolidation phase that leads to transplant; these patients were randomized 1:1 to receive either 2 blocks of chemotherapy or 2 cycles of blinatumomab.

After a median follow-up of 1.4 years, the results showed[1]:

- 59% of the patients in the blinatumomab group had disease-free survival, which was the primary end point, compared with 41% for the chemotherapy group.
- Overall survival also favored the blinatumomab group over the chemotherapy group, 79% versus 59%
- 73% of the blinatumomab group were able to proceed to transplant, compared with 45% of the chemotherapy group.
- For patients with detectable MRD after the month of chemotherapy reinduction, 79% of those receiving blinatumomab achieved undetectable MRD, compared with 21% of those who continued chemotherapy.

"Based on our study, it appears that blinatumomab is a much more effective bridge to transplant for this patient population, leading to a much larger portion of patients who are actually able to receive a bone marrow transplant," Brown said in a statement.[3] "We believe that is the reason for the striking improvement in survival among patients who received blinatumomab."

A bispecific T cell engager, or BiTE, blinatumomab binds specifically to CD19, a protein on the surface of B cells, and to CD3, a protein expressed on the surface of T cells, causing the T cells to kill leukemia cells. When it was approved, blinatumomab reached the market at a list price of $178,000 for 2 cycles, making it one of the most expensive cancer drugs on the market at the »

BROWN
Patrick A. Brown, MD, Johns Hopkins University Kimmel Comprehensive Cancer Center

BRODSKY
Robert Brodsky, MD, director, Division of Hematology, Johns Hopkins School of Medicine

time.[4] However, a July 2017 analysis in the *Journal of Medical Economics* found it to be cost-effective based on its survival and quality-of-life benefits.[5]

Importance of Reducing Infection Risk

In response to a question from *The American Journal of Managed Care®*, Brown explained that studies show the burden of life-threatening infection from chemotherapy in B-ALL falls more heavily on the adolescent and young adult (AYA) population compared with older patients. "It's likely that the impact of improvement in survival with immunotherapy in the relapse setting may be particularly important in the AYA population, since the burden of infection seems to be greatest in those patients," he said.

Brown said during the press briefing that the survival benefits for blinatumomab were driven in part by the reduced infection risk, as there were 4 infection-related toxicity deaths among patients in the traditional chemotherapy group and none in the blinatumomab group. The researchers also compared adverse events (AEs) of grade 3 or higher for the final 2 cycles of chemotherapy in the control group and the 2 cycles of blinatumomab, tallying these results[1]:

- Febrile neutropenia: chemotherapy 44% (1st cycle)/46% (2nd cycle) vs blinatumomab 4%/0%; P <.001 for both cycles
- Infections: chemotherapy 41%/61% vs blinatumomab 10%/11%; P <.001 for both cycles
- Sepsis: chemotherapy 14%/21% vs blinatumomab 1%/2%; P <.001 for both cycles
- Mucositis: chemotherapy 25%/7% vs blinatumomab 0%/1%; P <.001 for first cycle/P = .16 for second cycle.

In the blinatumomab group, notable AEs included cytokine release syndrome (CRS). In the first cycle, CRS affected 22% overall, with 1% grade 3 or higher; in the second cycle, 1% overall, 0% grade 3 or higher. For other neurotoxicities, the rate was 14% overall, with 2% grade 3 or higher in the first cycle, and the rate was 11% overall and 2% grade 3 or higher in the second cycle. Investigators reported that all AEs were fully resolved.

"Based on our study, it appears that blinatumomab is a much more effective bridge to transplant for this patient population, leading to a much larger portion of patients who are actually able to receive a bone marrow transplant."

—Patrick A. Brown, MD,
Johns Hopkins University
Kimmel Comprehensive Cancer Center

Brown said future research in this area of treating pediatric B-ALL will include combining blinatumomab and checkpoint inhibitors, using immunotherapy to replace or augment reinduction chemotherapy, and using chimeric antigen receptor T cells to replace or augment hematopoietic stem cell transplant. ◆

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Apixaban Is Linked to Large Reductions in Major Bleeding, Recurrent VTE in Active Cancer

Maggie L. Shaw

PATIENTS WITH CANCER who took apixaban to prevent blood clots had a 37% reduction in major bleeding (MB) and a 39% reduction in recurrent venous thromboembolism (VTE) compared with those taking low-molecular weight heparin (LMWH), according to data presented on December 7, 2019, at the 61st American Society of Hematology Annual Meeting & Exposition in Orlando, Florida. Apixaban also had large reductions in VTE (32%) relative to warfarin.[1]

A subgroup analysis presented alongside the main study found that apixaban's benefits relative to LMWH held up across different types of cancer regardless of the risk level they present for VTE.[2] Apixaban is sold as Eliquis by Bristol-Myers Squibb/Pfizer.

Patients with active cancer—for this study, defined as cancer diagnosis or treatment in the 6 months before or 30 days after a VTE diagnosis—have a 4 to 7 times greater risk of developing VTE. To gain more real-world evidence on the effectiveness and safety of LMWH compared with vitamin K antagonists, which emerged in the last decade as a treatment of VTE, and non-VKA anticoagulants, a team of researchers led by Alexander T. Cohen, MBBS, MSc, MD, of King's College, London, evaluated the efficacy of apixaban, LMWH, and warfarin among patients with active cancer.

The investigators examined 3 groups of patients who started treatment within 30 days of their first VTE: 3393 apixaban users, 6108 LMWH users, and 4585 warfarin users. The mean ages were 65, 64, and 64 years, respectively. To evaluate rates of MB, clinically relevant non-MB (CRNMB), and recurrent VTE, the patients were followed to the earliest of 1 of 6 time points: health plan disenrollment, death, index therapy discontinuation, switch to another anticoagulant, study end, or a maximum of 6 months.[1]

The following results were reported:

- Apixaban had lower risks of MB, CRNMB, and recurrent VTE compared with LMWH, with a hazard ratio (HR) of 0.63 (95% CI, 0.47-0.86; $P = .003$) for MB, an HR of 0.81 (95% CI, 0.70-0.94; $P = .006$) for CRNMB, and an HR of 0.61 for recurrent VTE (95% CI, 0.47-0.81; $P = .001$).
- Apixaban had lower rates of recurrent VTE and modest reductions of MB and CRNMB compared with warfarin, with an HR of 0.68 (95% CI, 0.52-0.90; $P = .007$) for recurrent VTE, an HR of 0.73 (95% CI, 0.53-1.0; $P = 0.51$) for MB, and an HR of 0.89 (95% CI, 0.77-1.04; $P = 0.145$) for CRNM.

"Real-world evidence analyses such as this have the potential to provide additional insights into complex patient populations such as those with VTE and active cancer," Cohen said in a statement.[3] "Results from these analyses are a welcomed addition to the growing body of data around recurrent VTE in patients with active cancer."

In the second presentation, results from the subgroup analysis examined how apixaban affected recurrent VTE, MB, and CRNMB risk across different cancer types relative to warfarin and LMWN. Hematologic cancer, as well as those of the brain, pancreas, stomach, liver, lungs, and kidneys, are associated with a higher risk of VTE. Researchers used the Khorana risk score based on cancer type, blood counts, and body mass index to evaluate risk level and assess the safety of each therapy based on cancer type. Patients were categorized as having a very high risk of VTE, high risk of VTE, or other.

Results from the same real-world data set as the first abstract showed that those taking apixaban had a lower risk of recurrent VTE compared with warfarin and a lower risk of MB, CRNMB, and recurrent VTE compared with LMWH, consistent with the overall results. Researchers called for more studies to evaluate the role of anticoagulants in high-risk subgroups of patients with cancer who have VTE.[2]

Besides the risk of VTE, real-world evidence can be evaluated for other factors. Asked by *Evidence-Based Oncology*™ if the patient data could be evaluated to see whether those with comorbidities had different responses, Danny Wiederker, HEOR team lead at Pfizer, said in an email, "Comorbidities are always an important consideration in real-world evidence, given some may be important confounders that impact both the treatment decision and the outcomes of interest. That's why the Pfizer/BMS Alliance leverages the best research practices recommended by organizations like the International Society of Pharmacoeconomics and Outcomes Research that look to adjust for both comorbidities and patient factors, like age, gender, etc, that may impact outcomes."

"Real-world evidence analyses suchas this have the potential to provide additional insights into complex patient populations such as those with [venous thromboembolism] and active cancer."

—Alexander T. Cohen, MBBS, MSc, MD, King's College, London

He said the study being presented is the inverse probability of treatment weighting to adjust for confounding while including the broadest possible patient population.

"Our approach generally is to start with the broad population and then drill down into subgroups as we are also highly interested in better understanding in which patient populations there is even more unmet need and more opportunity to improve outcomes," Wiederker said. "We have conducted the first subgroup analysis presented as the second oral presentation stratifying based on the risk of recurrent VTE level, but we also have interest in other subgroups and are exploring opportunities for additional analyses." ◆

COHEN
Alexander T. Cohen, MBBS, MSc, MD, King's College London

WIEDERKER
Daniel Wiederke, HEOR team lead, Pfizer

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Real-World Results Show Medicare Costs Drop After Completion of CAR T-Cell Therapy

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Karl M. Kilgore, PhD, Avalere Health

ALVARNAS
Joseph Alvarnas, MD, City of Hope, Duarte California

STATLER
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MOST MEDICARE PATIENTS treated with chimeric antigen receptor (CAR) T-cell therapies in the first year after FDA approval for diffuse large B-cell lymphoma fared well after the procedure, according to an Avalere Health study presented at the 61st American Society of Hematology Annual Meeting and Exposition in Orlando, Florida.

More than half of the patients treated with this expensive revolutionary therapy had comorbidities common in seniors, such as heart disease or renal problems, that might have kept them out of clinical trials. But 6 months after treatment, hospital stays dropped 17% from pretreatment levels. And healthcare costs 6 months after CAR T-cell therapy, based on Medicare Part A and B, were 39% lower than they were in the 6 months before treatment, said lead study author Karl M. Kilgore, PhD, who shared results from 207 patients in a press briefing on December 7, 2019.

The study is the first claims analysis from Medicare patients who received CAR T-cell therapy in the year after October 1, 2017.[1] The FDA approved Novartis' tisagenlecleucel (Kymriah) in August, followed by Gilead's axicabtagene ciloleucel (Yescarta), in October 2017. Both are approved to treat adults with relapsed or refractory large B-cell lymphoma.[2]

Medicare patients in the Avalere study were more than a decade older than the median age of patients in clinical trials, yet many had good outcomes. "Our findings offer evidence that older patients with multiple comorbidities can be treated successfully with CAR T," he said in a statement.[3] "While we don't know the long-term outcomes yet, nearly three-quarters of the patients were still alive 6 months posttreatment."

Kilgore said this is the first analysis to use real-world evidence—in this case, Medicare claims—to examine how CAR T-cell therapy works in older patients with other health issues.

Although the Avalere study found a significant decline in both healthcare utilization and cost, Kilgore was clear that this "is not a cost-effectiveness study," meaning it was not designed to evaluate the healthcare savings seen after treatment against the cost and benefits of treatment itself. CAR T-cell therapy in this indication costs $373,000 just for the specially engineered therapy manufactured from a patient's own cells. Administration costs, including the cost of treating adverse events, can easily drive the total price tag closer to $1 million.

Medicare and academic centers that offer CAR T-cell therapy have battled over reimbursement rates for more than a year, and while payment is set to rise in 2020, a commentary in the *Journal of Clinical Oncology* in November estimated that centers lose $300,000 on every Medicare patient they treat.[4]

Highlights from the Avalere study showed[1]:

- The median age of the Medicare patients was 71, compared with 56 to 58 years of age in clinical trials, and 51% of individuals in the Medicare group had 1 or more chronic conditions.
- Results after 177 patients showed the drop in per-patient per-month healthcare utilization costs in Medicare Part A and B fell from $9749 in the period 6 months before CAR T-cell therapy to $7121 in the 6 months after therapy. Kilgore said in an interview with *Evidence-Based Oncology*™ that Part D data had not been released in time for the American Society of Hematology meeting and would be analyzed separately.
- Six months after treatment, emergency department visits dropped by 45%, and the number of patients visiting the emergency department dropped by one-third.
- The study shed light on the healthcare needs of Medicare patients receiving CAR T-cell therapy—the average hospital stay for the procedure is 17 days. Less than half needed time in the intensive care unit; those that did stayed 13 days.

Kilgore noted that reimbursement methods to hospitals performing CAR T-cell treatment vary, with some subject to the acute inpatient prospective payment system rule, while others are exempt.[5] The Avalere study found that the Centers for Medicare & Medicaid Services, on average, is reimbursing under the inpatient prospective payment system about $422,000, compared with $467,000 in the outpatient setting.[3]

Joseph Alvarnas, MD, an oncologist/hematologist who serves as vice president of government affairs and senior medical director for employer strategy for City of Hope in Duarte, California, and is editor-in-chief of *Evidence-Based Oncology*™, said that while the Avalere analysis is not a cost-effectiveness study or a comparative effectiveness model, "These data add to other data sets that continue to validate the idea that there is a real value proposition for these therapeutics, that provides a path toward developing an economically sustainable model for treating this population of patients."

The authors acknowledge that the Medicare patient sample remains small and that it may not represent a broader patient population. Kilgore has received research funding from Kite Pharma, which developed the CAR T-cell product that Gilead acquired and launched.

Avalere's results were part of a set of abstracts that highlighted results involving disparities in care. Other results include:

- A study of 1040 patients with acute myeloid leukemia (AML), presented by Abby Statler, PhD, MPH, of Cleveland Clinic, found that issues with renal function appear to be a barrier to enrollment in clinical trials for African Americans. However, there is no association between clinically insignificant renal lab values and response to treatment or overall survival (OS), so the study recommends adjusting trial eligibility criteria to reduce racial disparities in enrollment.[6]
- Lena E. Winestone, MD, MSHP, of the University of California, San Francisco, presented data that show children with AML from middle- and high-income areas experience a 25% lower mortality risk compared with those from low-income areas (OS, crude hazard ratio [HR], 0.74; 95% CI, 0.62-0.89; adjusted HR, 0.79; 95% CI, 0.63-0.99). Clinical trial data were matched with zip-code data as a proxy for income, and the authors of the study concluded that "zip-code–based low socioeconomic status is an independent risk factor for mortality in pediatric AML."[7]
- Anita D'Souza, MD, MS, of the Medical College of Wisconsin at Milwaukee, presented a large study of autologous hematopoietic cell transplantation in older adults with multiple myeloma (at least 70 years of age) and found that these older patients can safely undergo the transplant procedure with the same benefits that are seen in younger patients. Adjusted results show that compared with patients aged 60 to 69 years, those 70 years of age or older had similar

nonrelapse mortality, with an HR of 1.3 (95% CI, 1-1.7; *P* = .06); progression-free survival; HR, 1.06 (95% CI 1-1.2, *P* = .2); and OS, with an HR of 1.2 (95% CI, 1-1.4; *P* = .02).[8] ◆

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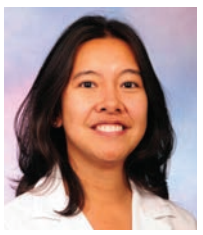
Most Patients With Medicare Need Additional Financial Assistance to Get Novel Oral Therapies

Maggie L. Shaw

IT'S NO SURPRISE THAT oral novel therapeutics (ONTs) used to treat hematologic malignancies are expensive. What is surprising is that most patients receiving Medicare require additional financial assistance to help pay for these therapies each month, according to data presented on December 7, 2019, at the 61st American Society of Hematology Annual Meeting and Exposition in Orlando, Florida.



SEYMOUR

Karmanos Cancer Institute, in Detroit, Michigan, established a specialty pharmacy to help alleviate the financial burden many patients face when paying for their ONTs. The pharmacy helps streamline the often frustrating and complex process of obtaining prior authorization (PA) and determining patient payment obligation. Federal regulations prohibit Medicare beneficiaries from using co-pay cards to decrease their out-of-pocket costs because CMS believes that doing so will drive up overall costs for insurers. Karmanos then goes one step further on behalf of patients, automatically applying for financial assistance when necessary, in the form of co-pay cards and foundation grant funding, before determining what a patient will ultimately have to pay and when their drugs will be delivered.

Hoping to establish patterns of cost and the need for financial assistance since the specialty pharmacy was established, first author Erlene K. Seymour, MD, and her team used a retrospective data review from March 2018 through May 2019. During this time, the prescription claims totaled over $2 million. Data were gathered on the following: drug prescribed, type of insurance (Medicare, Medicaid, private), insurer cost, final patient cost sharing, costs covered by foundation grant assistance or co-pay cards (if needed), and the number of days between written prescription and (1) PA and (2) drug delivery to patient (see **Table**).[1]

Overall, 35% of the patients needed help with payment, most of which was achieved through foundation grants versus co-pay cards (26% vs 9%). Medicare accounted for half of all reimbursement; 40% of these patients needed foundation grant assistance, and 19% ended up with high co-pays of $100 or more. Fifty-two percent of patients had Medicare; 33%, private coverage; and 17%, Medicaid. From most to least costs covered, Medicare topped the list by paying half, followed by foundation grant assistance, the patients themselves, and co-pay cards. Also, neither insurance type nor grant need factored into time needed for PA or drug delivery at 1 and 7 days, respectively.

"Of the $2 million in total drug costs, 4% was total patient co-payments, which presented as high co-pays for many patients. Thirty-six percent of these patients received financial assistance, mostly through foundation grants," Seymour said in an email to *Evidence-Based Oncology*™. "Karmanos Specialty Pharmacy implemented an efficient process of applying for financial assistance, which decreased total patient cost by 79%. However, the fact that so many required assistance or continued to pay high co-pays emphasizes the need to cap these costs for our patients." ◆

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TABLE. Costs, Distribution of Financial Assistance, and Time to Drug Delivery by Insurance Type via KCI Specialty Pharmacy[1]

Insurance Type[a]	Total Costs				Financial Assistance		PTS With High Cost >$100 Without Financial Assistance	Time From 1st Prescription to Prior Authorization Median days (range)	Time From 1st Prescription to Delivery Median days (range)
	Insurer	Financial Assistance		Patient Cost	Foundation Grants	Co-Pay Cards			
		Foundation Grants	Co-Pay Cards						
Medicare N = 52 pts	$1,118,464	$44,010	$0	$19,518	21 PTS (40%)	0 PTS	10 PTS (19%)	0 (0-47)	5 (1-52)
Private N = 33 pts	$651,554	$8937	$8486	$4290	5 PTS (15%)	9 PTS (29%)	1 PTS (3%)	1 (0-23)	6 (1-35)
Medicaid N = 17 pts	$281,886	$0	$0	$1	0 PTS	0 PTS	0 PTS	0 (0-48)	7 (0-56)

KCI indicates Karmanos Cancer Institute; pts, patients.
[a]2 patients switched insurance, N = 102

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Brukinsa™
zanubrutinib 80 mg capsules

BRUKINSA™ (zanubrutinib) IS A KINASE INHIBITOR INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Learn more at BRUKINSA.com

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose.

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.

ADVERSE REACTIONS

The most common adverse reactions in > 10% of patients who received BRUKINSA were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see Brief Summary of full Prescribing Information on the following pages.

BeiGene

BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA™ (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. 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 (8.1)]*.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 320 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year.

In this pooled safety population, the most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥ 75 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a CLcr ≥ 30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection¶	39	0
	Pneumonia§	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rashǁ	36	0
	Bruising*	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage†	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction
* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis
† Hemorrhage includes all related terms containing hemorrhage, hematoma
‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis
§ Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral
ǁ Rash includes all related terms containing rash
¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis†	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† Asymptomatic lymphocytosis is a known effect of BTK inhibition.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 5: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, 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. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA. 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 BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

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Patient-Reported Outcomes Are Top of Mind at Annual Meeting

Maggie L. Shaw

Symptom burden, functional ability, and quality of life are necessary considerations when treating hematologic malignancies in older patients.

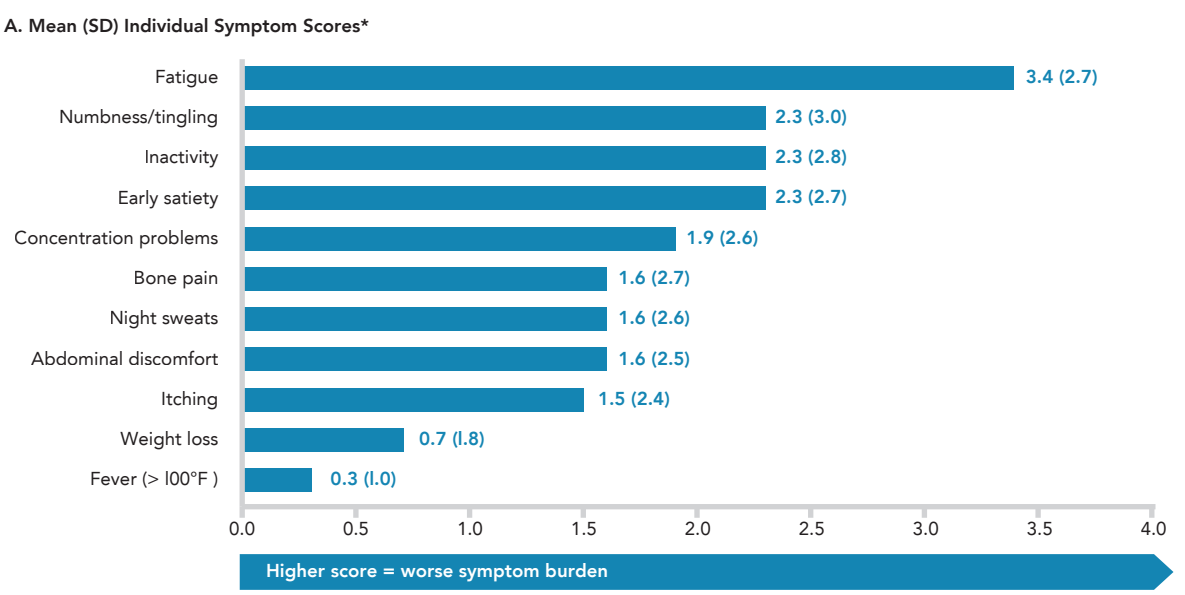
DURING ORAL ABSTRACT SESSIONS at the 61st American Society of Hematology Annual Meeting & Exposition in Orlando, Florida, results from the MOST and CLL14 trials were presented on older patients being treated for essential thrombocythemia (ET)/myelofibrosis and chronic lymphocytic leukemia (CLL), respectively. Results showed significant symptom burden, particularly from fatigue.

Both studies covered older patients, with a median age of 70 years (range, 19-93) for patients in MOST (80% were at least 60 years of age)[1] and at least 71 years for patients in CLL14.[2] They both also used the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) to evaluate health-related quality of life (QOL) (functional ability), with MOST also using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) for symptom burden and CLL14, the MD Anderson Symptom Inventory (MDASI). Patients were asked to report on symptom burden, functional status, and QOL at regular intervals throughout their treatment using provided questionnaires. These patient-reported outcomes (PROs) are meant to inform a greater understanding of how to improve QOL affected by treatment.

In MOST,[1] patients on ET-directed therapy were observed for 36 months, and their data (also known as a score) were collected every 6 months. High scores indicated good results for functional status and QOL, but a significant symptom burden. The mean (SD) TSS score (range, 0-100 overall; 0-10 per symptom) was 17.1 (15.6), with women faring worse than men (18.5 [15.8] vs 14.2 [14.9]). Fatigue had the highest individual mean symptom score (3.4 [2.7]), topping also the EORTC QLQ-C30 scale for severity, at 29.6 (25.8). The mean global health status/QOL score was 72.7 (21.9) (**Figure 1**). Men had overall higher functioning scores and less symptom burden than women.

In CLL14,[2] 432 patients received chlorambucil/obinutuzumab (Gazyva) (CIbG) or venetoclax/obinutuzumab (VenG). They were observed for a median 28.1 months, and their data (score) were collected every 3 months during follow-up. Again, high scores indicated good functional status and QOL, but a great symptom burden. EORTC physical and role function scores were a mean (SD) 75.9 (± 20.1) and 76.9 (± 19.4) in the CIbG and VenG arms (216 patients each), respectively, when treatment started, whereas QOL was 63.6 (± 21.0) and 60.3 (± 20.5), respectively. The VenG treatment group

FIGURE 1. Fatigue Most Frequently Reported Symptom in MOST

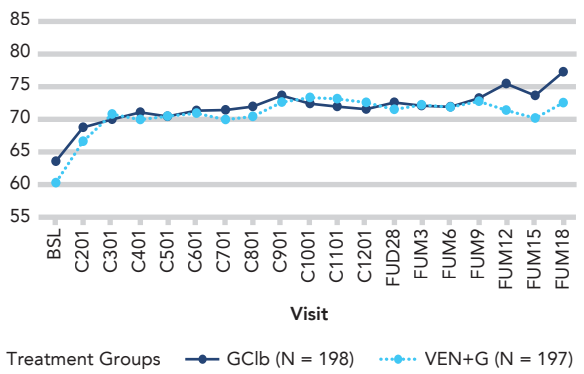


EORTC QLQ-C30 indicates European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; QOL, quality of life; SD, standard deviation.

*Each item was scored on a scale from 0 (absent) to 10 (worst imaginable). Only evaluable patients with MPN-SAF TSS and MPN-SAF numbness/tingling data (n = 768) were included.

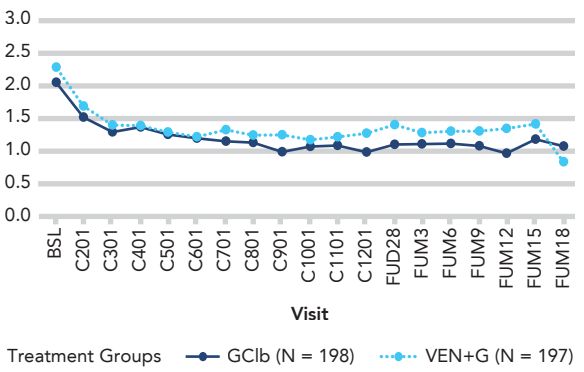
†All scores were standardized with linear transformation to Oto 100. Only evaluable patients with EORTC QLQ-C30 data (n = 794) were included.

FIGURE 2. Mean Change Over Time: Global Health Status/QOL



GClb indicates chlorambucil/obinutuzumab; QOL, quality of life; VEN+G, venetoclax/obinutuzumab.

FIGURE 3. Mean Change Over Time: Symptom Interference



GClb indicates chlorambucil/obinutuzumab; VEN+G, venetoclax/obinutuzumab.

fared better more quickly, however, with meaningful improvement in QOL seen by cycle 3 of treatment compared with cycle 8 for the CIbG group (**Figure 2**).[3] For MDASI, CLL (1.5 [± 1.2] and 1.6 [± 1.3]) and core cancer (1.5 [± 1.4] and 1.8 [± 1.7]) symptoms and symptom interference (2.1 [± 2.3] and (2.3 [± 2.3]) remained low and similar from baseline through follow-up for the VenG and CIbG groups, respectively (**Figure 3**).[3] Overall, functional status and QOL did not worsen and symptom severity remained low among both groups, with dyspnea being the most severe symptom at baseline (24.8 [± 27.76]), compared with during treatment and follow-up.

Investigators from the MOST trial believe that "future analyses from this trial will continue to increase understanding of the symptom burden and its impact on QOL in patients with ET," whereas CLL14 investigators note, "As elderly patients with CLL typically experience impairment of QoL, particularly when suffering from various other conditions, such improvement should be considered a main therapeutic goal." ◆

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Patient-Reported Outcomes Are Considered During FDA Clinical Reviews

Maggie L. Shaw

DISEASE SYMPTOMS, symptomatic adverse events, and physical function top the list of patient-reported outcomes (PROs) from cancer clinical trials of interest to the FDA during application reviews for both new products and new indications for existing medications.[1] During the recent 61st American Society of Hematology Annual Meeting & Exposition in Orlando, Florida, for benign and malignant hematology indications, data were presented that show just how often the FDA considers PROs during clinical review, when PROs are included in product labels, and what the PROs referenced.

Investigators from the FDA and the Center for Biologics Evaluation and Research (CBER) gathered PRO data for approvals between 2017 and 2018 from the Center for Drug Evaluation and Research in the Office of Hematology and Oncology Products and CBER, as well as determined the frequency with which those data were included on clinical study reports (CSRs)[2], final FDA review, and drug labels. The FDA handed down 64 approvals during the study period (31 new molecular entity [NME][3] and 33 supplemental applications).

The investigators determined that PRO data were included on 30% (3/10) of the CSRs for benign hematology NMEs and biologics license applications (BLAs) and 47% (7/15) of CSRs for malignancy applications. However, the FDA subsequently included that data in its clinical review for 9 submissions (3, benign; 6 malignant), and labels for Hemlibra (emicizumab; Chugai) and Rituxan Hycela (rituximab/hyaluronidase human; Genentech/Biogen) ultimately incorporated the data. Hemlibra[4] treats hemophilia A, and Rituxan Hycela[5] treats relapsed or refractory follicular lymphoma (FL), previously untreated FL, nonprogressing FL, previously untreated diffuse large B-cell lymphoma, and previously untreated and treated chronic lymphocytic leukemia (CLL).

PRO data were also included on 38% (3/8) of the CSRs for supplemental benign hematology indications and 65% (13/20) for malignant indications. The FDA went on to include that data in its clinical review for 15 submissions (3, benign; 12, malignant), and labels for Feraheme (ferumoxytol; AMAG)[6] and Imbruvica[7] (ibrutinib; Pharmacyclics/Janssen Biotech) include the data. Feraheme treats iron deficiency anemia, and Imbruvica treats mantle cell lymphoma, CLL, CLL/small lymphocytic leukemia with 17p deletion, Waldenström's macroglobulinemia, marginal zone lymphoma and chronic graft versus host disease.

Overall, more labels for benign indications (33% [1/3], NMEs and BLAs; 33% [1/3], supplemental) included PROs data than did those for malignant indications (16% [1/6] and 8% [1/12], respectively), and these data covered disease symptoms and physical function.[8]

The FDA is currently developing guidelines for the use of PROs in cancer clinical trials. ◆

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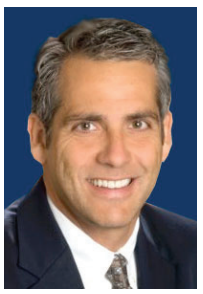
INTERVIEW

Data Show Fixed-Dose Daunorubicin Plus Cytarabine Leads to Fewer Inpatient Days for Patients With sAML

Mary Caffrey



IANNONE

Robert Iannone, MD, MSCE, executive vice president, research and development, Jazz Pharmaceuticals

DATA PRESENTED AT the 61st American Society of Hematology (ASH) Annual Meeting and Exposition on the fixed-dose combination of daunorubicin and cytarabine, known as CPX-351 and sold as Vyxeos by Jazz Pharmaceuticals, led to fewer inpatient days than patients treated with the conventional regimen for secondary acute myeloid leukemia (sAML).[1]

The results were based on data from the Premier Healthcare Database and involved 195 patients treated with CPX-351 and 160 eligible for CPX-351 but treated with the 7+3 regimen, which consists of cytarabine administration for 7 days and short infusions of anthracycline for the first 3 days. By contrast, CPX-351 is a liposome-encapsulated combination of daunorubicin and cytarabine at a synergistic 1:5 molar ratio.

The abstract presented by Kwanza Price, MPH, of Jazz Pharmaceuticals, gathered data from August 1, 2017, and February 28, 2019, capturing the first 19 months of claims data after the biotech received FDA approval for its fixed-dose therapy for 2 types of poor-prognosis acute myeloid leukemia (AML).[2]

Patients captured in the retrospective observational study had a median age of 68 years for the CPX-351 group and a median age of 61 years for the 7+3 group. Male patients made up 62.6% of the CPX-351 group and 55% of the 7+3 group. White patients comprised 72.3% of the patients in the CPX-351 group and 75% of the patients in the 7+3 group. The median length of follow-up was 136 days for the CPX-351 group and 126 days for the 7+3 group. Results from the database study show:

The median inpatient length of stay per patient year (PPY) was shorter in the CPX-351 group compared with those in 7+3 group (nominal $P = .068$).

Although the median hospital costs PPY in the CPX-351 group were higher (nominal $P < .001$), the nondrug medical cost PPY was not higher (nominal $P = .785$).

Separate data presented at ASH showed that CPX-351 improved overall survival (OS) in patients with therapy-related AML (t-AML).[3] CPX-351 also improved OS in patients who had a stem cell transplant compared with patients who underwent a transplant, treated with the traditional 7+3 regimen in the subgroup of patients with AML who had a history of myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm who achieved complete response or complete response with incomplete neutrophil or platelet recovery.[4]

Evidence-Based Oncology™ (*EBO*) asked Robert Iannone, MD, MSCE, executive vice president of research and development at Jazz Pharmaceuticals, to discuss the results presented at ASH:

EBO: The different data sets presented at ASH showed that CPX-351 extends survival time relative to standard of care (7+3) while also reducing the amount of time patients spend in the hospital. What has been the response from physicians regarding these findings?

IANNONE: While we don't have specific feedback to share, the ability to extend survival time— and potentially provide older patients with sAML a better chance for remission, which can help them prepare for transplant—is a positive, and an advancement over traditional chemotherapy. Combined with a possible reduction in the amount of time hospitalized, we are confident in the value that Vyxeos provides to physicians as well as to patients.

EBO: Can you discuss the ability of CPX-351 to address areas of unmet need?

IANNONE: Vyxeos is the first and only chemotherapy treatment option for patients diagnosed with 2 types of secondary (sAML), t-AML and AML with myelodysplasia-related changes. Vyxeos provides these patients with a better chance for remission, which can help them prepare for transplant, representing an advancement over traditional chemotherapy. Vyxeos has also been shown to deliver significant improvement in both OS and complete remission rates compared to the current standard of care, 7+3 (daunorubicin and cytarabine), based on robust phase 3 program data.

As the leukemia treatment landscape evolves, we understand the potential of combination therapy for this difficult-to-treat patient population. We are committed to exploring the full potential of Vyxeos as the key component in combination with other therapies to address currently unmet needs.

EBO: What is the importance of these findings to the ability of physicians to get patients to transplant?

IANNONE: As mentioned, for older patients with sAML, Vyxeos provides a better chance for remission compared to traditional chemotherapy, which can help them prepare for transplant.

It's important for patients and oncologists to understand all treatment options. For appropriate older patients with sAML, intensive chemotherapy followed by hematopoietic stem cell transplant is a treatment option with curative intent.

EBO: Can you describe your conversations with payers and what questions they have? Are you encountering barriers to prior approval or access?

IANNONE: We can't share any specifics of our conversations with payers. We are pleased that the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for AML were updated in September 2019, granting Vyxeos category 1 for patients with t-AML or antecedent MDS/chronic myelomonocytic leukemia or AML with myelodysplasia-related changes who are 60 and older. Vyxeos is the only category 1 recommendation for these patients. We are pleased with the access Vyxeos has, and for the overwhelming majority of accounts across the country, we have not encountered barriers to prior approval or access.

EBO: What are the next research questions on the horizon for CPX-351?

IANNONE: We are very interested in the potential of combination therapy, and we're committed to exploring the full potential of Vyxeos as the key component in combination with other therapies. Planned studies of Vyxeos in combination with other treatments—including venetoclax, gemtuzumab, and various targeted therapies—will explore the potential for these combination treatments to reach more patients.

AJMC

JAMA Study Finds No Link Between Talc Powder and Ovarian Cancer
ajmc.com /link/4441

We're also continuing to explore different dosages, strengths, and schedules of Vyxeos with the goal of adjusting for patient ability to manage treatments, in particular for both fit and unfit patients, as well as standard- and high-risk AML in newly diagnosed patients.

MDS also remains an area of great interest to Jazz, and we're working to test Vyxeos in this population.

EBO: Finally, we're curious—what is the origin of the name Jazz Pharmaceuticals?

IANNONE: In music, jazz is the art of harnessing individual talents through collaboration, improvisation, and constant evolution. It's unique in its sound and composition, and the connections it creates are personal. In healthcare, it is much the same.

We chose the name Jazz because it reflects not only how we approach our business but also—and more importantly—how we approach our responsibility to change people's lives. ◆

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At ASH, Data on Truxima Underscore the Biosimilar's Safety and Efficacy

Kelly Davio

CELLTRION AND TEVA'S BIOSIMILAR RITUXIMAB, CT-P10 (Truxima), recently launched in the United States. The product is the first rituximab biosimilar to become available to patients in the United States,[1] and during the 61st meeting of the American Society of Hematology (ASH) held from December 7-10, 2019, a pair of research teams presented data that highlight the biosimilar's safety and efficacy in patients with lymphoma.

New phase 3 data show similar safety and efficacy between CT-P10, reference

First, a team presented on updated phase 3 study results from a clinical trial of the biosimilar in 140 patients with newly diagnosed advanced-stage follicular lymphoma.[2] Previously reported results from the same trial showed similarity between the biosimilar and the reference product, Rituxan, in terms of progression-free survival (PFS) and overall survival (OS) at a median follow-up of 22.6 months.

In the study, 70 patients received biosimilar rituximab with cyclophosphamide, vincristine, and prednisone, and 70 patients received the reference with the same regimen, for 8 cycles. Of these patients, 62 in the biosimilar group and 60 in the reference group entered the rituximab monotherapy maintenance period after induction therapy, and 46 and 38 patients, respectively, completed the maintenance period of 2 years. After 2 years, patients were followed for tumor evaluation up to 3 years from the last patient's first infusion.

For investigator-assessed PFS, time to progression (TTP), and OS, medians have not been reached in either group (median follow-up durations: 40 months in the CT-P10 group and 39 months in the reference group).

There were no significant differences between the groups in terms of PFS (hazard ratio [HR], 1.33; 95% CI, 0.67-2.63; 4-year PFS for CT-P10, 60.9%; 95% CI, 46.5%-72.5%; 4-year PFS for reference, 54.7%; 95% CI, 36.1%-70.0%).

There were also no significant differences in TTP (HR, 1.17; 95% CI, 0.58-2.37; 4-year TTP for CT-P10, 64.2%; 95% CI, 49.4%-75.7%; 4-year TTP for reference, 55.8%; 95% CI, 36.8%-71.1%).

OS was comparable between the groups (4-year OS for CT-P10, 88.0%; 95% CI, 77.5%-93.8%; 4-year OS for reference, 93.3%; 95% CI, 83.2%-97.4%; $P = .287$).

In total, 30% of patients in each group experienced disease progression. Five patients in the biosimilar group and 2 patients in the reference group died during the study period. No new safety signals were identified, and similar numbers of patients in each group experienced at least 1 treatment-emergent adverse event.

Rapid infusion with CT-P10 is well tolerated

Second, another group of researchers reported on a postauthorization safety study of the biosimilar that is currently underway in several European nations.[3] The study concerns rapid infusion of the biosimilar, over a period of 90 minutes or less, during routine clinical practice.

In Europe, the recommended protocol for rituximab infusion is a slow initial infusion rate with a gradual upward titration, but rapid infusion is often used in second or subsequent infusions for patients who had no serious complications with a first infusion.

In the study, 112 patients with lymphoma who had between 1 and 4 prior infusions with CT-P10 were given subsequent rapid infusions over a 6-month observation. In total, 19 patients experienced 1 or more infusion-related reactions (IRRs). Of these patients, 9 had 1 IRR, 5 had 2 IRRs, and 5 had 3 or more IRRs.

The best responses to rituximab therapy during the observation period were complete response in 74% of patients, partial response in 21% of patients, stable disease in 3% of patients, and progressive disease in 2% of patients, said the investigators. ◆

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Data on Complement Inhibitors and Proposed Biosimilars Featured at ASH

Kelly Davio

ECULIZUMAB, A C5 COMPLEMENT INHIBITOR, has changed the treatment landscape for several rare diseases, including paroxysmal nocturnal hemoglobinuria (PNH), myasthenia gravis, and atypical hemolytic uremic syndrome. However, the drug, sold by developer Alexion as Soliris, is among the most expensive biologic therapies in the world—carrying a cost of approximately $500,000 per patient per year[1]—and that cost has an impact on patient access.

Multiple biosimilar developers are taking aim at eculizumab, however, and at the same time, Alexion is continuing to invest in a longer-acting successor to eculizumab as biosimilars draw closer. During the 61st meeting of the American Society of Hematology (ASH), investigators reported on eculizumab, a prospective biosimilar, and the long-acting ravulizumab.

Investigators report on PK and ADAs for proposed biosimilar eculizumab, ABP 959

Amgen is developing ABP 959, a proposed biosimilar to eculizumab, and the product has previously been reported to have pharmacokinetic (PK) and pharmacodynamic equivalence with the reference Soliris.[2]

During ASH, researchers reported on an assessment of the relationship between PK parameters and antidrug antibodies (ADAs) for the proposed biosimilar and the reference.[3] Their data derive from a randomized, double-blind, single-dose, 3-arm, parallel-group study in healthy male volunteers.

In the study, the 219 participants were randomized to receive 300 mg of either the biosimilar (n = 71), its US-licensed reference (n = 74), or its EU-licensed reference (n = 74), and serum samples for PK evaluation were collected over 57 days.

No neutralizing antibodies were detected during the study. At any time, the incidence of binding ADAs was 9.9% in the biosimilar group, 6.9% in the US reference group, and 9.5% in the EU reference group. At the end of the study, 1.9% of participants had binding ADAs, with 1.4% in the biosimilar group, 2.9% in the US reference group, and 1.4% in the EU reference group testing positive for these ADAs.

In those who had binding ADAs, PK was within the same range as it was in those without any ADAs detected, per the authors. Furthermore, the incidence of ADAs was similar between products and did not affect the overall PK similarity assessment.

Relatively few US patients with PNH start treatment with eculizumab

Complement inhibition is becoming the standard of care in treating PNH, but given the fact that PNH is a rare disease, little is known about how patients are managed after diagnosis in real-world practice.

Using Truven US MarketScan commercial and Medicare data from 2015 to 2018, researchers sought to estimate the incidence and prevalence of PNH and to describe real-world treatment in patients who are newly diagnosed with the blood disease.[4]

They found that the incidence rate over the study period was 5.7 per 1,000,000 person-years, or 257 new diagnoses. Over a mean follow-up time of 385.6 days (SD, 253.2), just 10.3% of patients started eculizumab (95% CI, 6.3%-14.1%), initiating the drug 60.5 days (SD, 55.9 days) after diagnosis.

At 1 year, approximately one-third of patients had discontinued eculizumab or taken a break in treatment.

Future studies should explore factors related to initiating eculizumab, say the investigators, as well as those related to treatment persistence.

During the American Society of Hematology Annual Meeting and Exposition, investigators reported on the relationship between PK parameters and antidrug antibodies for the proposed biosimilar and the reference.

Successor to eculizumab proves effective, safe at week 52

Meanwhile, ravulizumab, Alexion's longer-acting C5 complement inhibitor that offers less frequent administration than eculizumab, was also the subject of a presentation of new data. Researchers presented 1-year safety and efficacy data from a phase 3 study in patients with PNH who had received eculizumab and transitioned to ravulizumab.[5]

Previously, treatment every 8 weeks with ravulizumab was shown to be noninferior to treatment every 2 weeks with eculizumab at 26 weeks.

The new data, up to 52 weeks, derive from an extension of the open-label trial. In the extension, patients who had received ravulizumab continued maintenance therapy, and those who had received eculizumab switched to ravulizumab. In total, 191 of 192 patients in the study entered the extension, and 96 were in the ravulizumab-only group, whereas the other 95 were in the switch group.

Patients in both groups showed a durable response for percent change in lactate dehydrogenase at 52 weeks; patients in the ravulizumab-only group had an 8.8% increase in lactate dehydrogenase from baseline (SD, 29%), whereas patients in the switch group had a 5.8% change (SD, 27%).

During weeks 0 to 26, 88% of patients in the ravulizumab-only group avoided transfusion, versus 87% of patients in weeks 27 to 52. In the switch group, 83% avoided transfusion during both periods.

During the extension period, 79% of patients in the ravulizumab-only group and 75% in the switch group had a treatment-emergent adverse event. Eight patients (8%) in the ravulizumab-only group and 5 (5%) in the switch group experienced serious adverse events, none of which led to discontinuation or death.

According to the researchers, ravulizumab continues to be well tolerated at week 52, with no new safety concerns arising in the extension, and the drug appears to have durable efficacy. ◆

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Produced by Laura Joszt and Matthew Gavidia

NOTE: this section has been edited for clarity

Lena Winestone, MD, Assistant Professor of Pediatrics, University of California, San Francisco

What have you found regarding how neighborhoods, specifically if they are those with low income and low education, impact survival in children with cancer?

We found that children with acute myeloid leukemia, a type of leukemia that affects children, have an increased risk of mortality if they come from a low-income or high-poverty neighborhood. In particular, we looked at that and broke it down in several different ways. We looked at the risk of relapse and found that there was an increased risk of relapse among those patients. And in addition, we found that they had a higher risk of toxicity that led to mortality among that patient population.

Finally, we looked at early mortality as a marker, potentially, of access to care, and found that low-income patients also have a substantial increased risk of early mortality or death during the first course of chemotherapy, suggesting that a component of what's going on may be related to access. ◆

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Michael Wang, MD, Professor, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center

What were your findings of using ibrutinib as a frontline treatment in patients in mantle cell lymphoma (MCL), and how might these findings change treatment decision making for these patients?

A perfect example of the toxicities of chemotherapy is the Hyper-CVAD [cyclophosphamide, vincristine, doxorubicin and dexamethasone] chemotherapy. Hyper-CVAD has been used for young patients newly diagnosed with mantle cell lymphoma. [To receive] Hyper-CVAD, you have to be in the hospital for 7 days, and then every month for 8 cycles, therefore, 8 months; and [approximately] 20% of patients after 15 years will develop another cancer. So, in order to cut down this therapy, you cannot say, "Hey, Dr Wang, today I have ibrutinib and I don't need Hyper-CVAD," that's not science. In science and clinical medicine, you cannot go from one extreme to the other extreme, you have to have a stepwise, gradual fashion.

So, WINDOW-1 clinical trial was designed—and it [was] presented in a poster[1]—we used an ibrutinib chemo-free window—why's it called a window, because before strictly heading to chemotherapy, we use rituximab-ibrutinib in the window period and we find out, after we get a complete remission, then we can use the chemotherapy with only 50% of the original dosage? The WINDOW-1 [clinical trial] utilized the chemo-free therapy upfront with ibrutinib and rituximab; in this case, the response rate is nearly 100%. The CR [complete remission] rate is between 92% to 94%, and you can see it in my poster and in my abstract. And my God, this is very powerful. And then, after patients are already in CR, we given them 4 cycles of chemo consolidation.

This, so far, is very successful. I have presented these data many times. We think we made progress to cut down the chemotherapy by incorporating, in a rational way, the chemo-free therapy. And of course, you never want to stop—the WINDOW-2 trial, in addition to ibrutinib and rituximab, we added another chemo-free agent, called venetoclax, which is targeting BCL-2—very powerful. And with this we try to drive the overall response rate to 100%. And then, if the patient is low-risk, there will be no chemotherapy needed. High-risk … blastoid, big tumors, and complex karyotype, 4 cycles. Low-risk none, intermediate[-risk] only 2 cycles. You can see from WINDOW-1 to WINDOW-2, gradually we are reducing chemo and try to further improve efficacy and decrease mortality from the toxicities. So, it's a very exciting time for chemo-free therapy. ◆

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C. Ola Landgren, MD, PhD, Professor of Medicine, Chief of Myeloma Service, Memorial Sloan Kettering Cancer Center

Carfilzomib is currently approved to treat patients with relapsed or refractory multiple myeloma—what did you find regarding the safety and efficacy of carfilzomib in newly diagnosed patients?

At [the 61st American Society of Hematology (ASH) Annual Meeting & Exposition] 2019, I'm the lead presenter, I'm the lead principal investigator for a phase 2 trial developed at [Memorial] Sloan Kettering, where we used the combination of carfilzomib with lenalidomide, dexamethasone, and also daratumumab. This is a phase 2 trial targeting newly diagnosed multiple myeloma patients.

The cohort I present uses once a week dosing with carfilzomib—it's a so-called 20/56 mg per meter squared dosing. So, 20 mg per meter squared, the first dose, and every other dose after that 56 mg per meter squared. So, once a week on a 4-week schedule means day 1, day 8, and day 15. Daratumumab is given standard dosing per the FDA label, which is 16 mg/kg body weight and is given weekly for the first 2 cycles and then is every other week for

another 4 cycles. And the last cycles are once every 4 weeks. This phase 2 trial includes a total of 8 cycles of therapy.

And the patient can go on [the trial], if they have a new diagnosis of myeloma, they fit the standard eligibility criteria, and it doesn't matter if they are younger or older, it doesn't matter if they are transplant candidates or not. Because the study is designed to look at minimal residual disease (MRD) as the primary end point after 8 cycles.

In the current literature, the best published MRD rates are in the range of around 30% or 40% or so—in this study that's not yet published, but presented at the ASH 2019, we report MRD rate of around 80%, and this is without bone marrow transplantation. ◆

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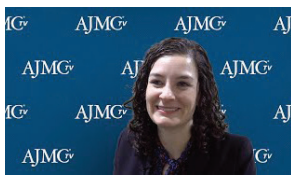
Lindsey Roeker, MD, Clinical Fellow, Memorial Sloan Kettering Cancer Center



What are some of the real-world unknowns regarding treatment patterns in CLL [chronic lymphocytic leukemia]?

Right now, we have basically prospective data showing the efficacy of a lot of novel agents—which is fantastic. But how they work in sequences is still an unknown question. We have small numbers of patients that have been treated with a novel agent after a novel agent. So, venetoclax after ibrutinib, we know that works. But the converse, whether ibrutinib works after venetoclax, is still somewhat of a question.

We have real-world data to support the use in people who have not previously been exposed to a BTK [Bruton tyrosine kinase] inhibitor, or for patients who have previously seen a BTK inhibitor but stopped because of intolerance. For patients who have actually previously failed a BTK inhibitor, it seems to be a less-effective strategy.

But that's all real-world data, retrospective. We don't have a prospective, large data set to support that practice. So, I think that's still a piece that we're trying to figure out. ◆

Banu Arun, MD, Medical Cncologist, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

Can you discuss the role of technology in expanding genetic counseling among patients with or at risk of developing breast cancer?

For patients with breast cancer, I think the question is, what technologies we can use to do the genetic counseling? You can do the traditional face-to-face counseling with the genetic counselor and the patient—that takes anywhere between 20 to 40 minutes—where pretest counseling is done and then you can order the test and you do the posttest counseling. So, that is what is widely used and what we've been doing.

But because of the increased number of patients, and the broadening testing guidelines, this might not work in especially high-volume clinics. So, what technology can we use? For example, something we implemented… is to do education by video, where the patient watches a preprepared video about genetics, family history, you know, indications for testing, [and] potential results for 10 to 15 minutes. And then the provider orders the test. And when the test results are positive, either pathogenic mutation or a VUS [variant of uncertain significance], then the patient is referred for genetic counseling and is meeting with the genetic counselor. So, that's how you combine the technology with face-to-face counseling.

Now, another way could be where the provider, and the counselor, is not involved at all. For example, doing web-based counseling. It is a one-way communication where the patient watches a video or a web-based presentation, and then a testing kit is sent home. The patient spits in it and then it's sent for it for genetic testing. So, there is no provider involvement. And some other technologies where a provider is not involved could include the chatbots and using some AI [artificial intelligence] technologies, but they're very new, and there are not too many studies about the outcome. But we, and other groups, are already doing some studies with using these technologies. ◆

Adam Olszewski, MD, Associate Professor of Medicine, Warren Alpert Medical School, Brown University

Why is palliative care not used earlier for patients with hematologic malignancies?

This is a very interesting and complex and heavily researched issue, actually. There are many studies that show patients with hematologic malignancies receive less end-of-life, less appropriate end-of-life care. So, they are receiving much more aggressive end-of-life care. And it is very easy to theorize about this, how this is happening, that, you know, patients with blood cancers have, that are often hanging in this state, where further treatment is always possible and remission is always possible. And that makes it very difficult for patients and for clinicians to actually recognize the moment where palliative care should come in to help manage patients' symptoms and maybe start thinking about really what are further goals of care and what the patient is expecting in terms of their realistic life expectancy.

A lot of research is showing that both clinicians have difficulty with this and patients may have difficulty with this as well. There's some prognostic discordance between patients and clinicians when discussing the prognosis of patients with leukemias and lymphomas, and myelomas as well. And then clinicians often have that perception that private care was developed for management of solid tumors, and that the needs of blood cancer patients may not be met fully with what has been developed. I feel that palliative care physicians are actually quite prepared to manage blood cancer patients, although they also need additional training because approaching a patient, you know a young person with multiple relapsed lymphoma or leukemia is quite different from often older patients with solid tumor that progressed as many lines of chemotherapy.

So, I think there are barriers on the clinician side, on the patient side, and there are also some systemic barriers. The study, it was shown, during this ASH, demonstrated that only a very, very small number of patients actually billed palliative care services early during the course of their disease—at least 30 days prior to their death. This was barely 2% even though it is increasing in the recent years.

But the difficulty that arises is also realization that the way we are billing and documenting these services is actually very difficult to capture later on through health services research. And that actually reflects challenges with billing and arranging and putting on this layer of palliative care over the layer of standard clinical care, which is still not fully recognized by insurers and organizations. So, I think there's also some systemic barriers that have to be overcome in integrating this truly. ◆

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