

AJMC[®]

THE AMERICAN JOURNAL OF MANAGED CARE[®]

Evidence-Based ONCOLOGY™

JANUARY 2019
VOL. 25 • NO. 1

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- REAL-WORLD EVIDENCE WITH AXI-CEL SHOWS CAR T SIMILAR TO ZUMA-1 FINDINGS, [SP11](#).
- ILLUMINATE: SUPERIOR PFS WITH IBRUTINIB COMBO EVEN IN HIGH-RISK UNTREATED CLL/SLL, [SP13](#).
- RUXOLITINIB BRINGS BETTER TREATMENT RESPONSE, LESS TOXICITY IN EARLY PRIMARY MYELOFIBROSIS, [SP15](#).
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TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA[®] (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS²

*Based on market share data from IMS from November 2016 to February 2018.

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

CLL
SLL

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

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)²
- CLL/SLL with 17p deletion²

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA[®] therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to IMBRUVICA[®] in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA[®]. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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

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

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA[®] therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA[®] in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA[®] treatment and follow dose modification guidelines.

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

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA[®] in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

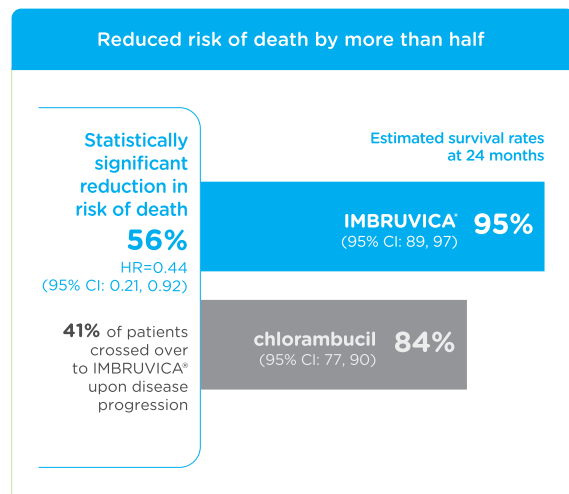
Monitor patients closely and treat as appropriate.

RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)^{2,3} Patients with 17p deletion were excluded³

EXTENDED OVERALL SURVIVAL²

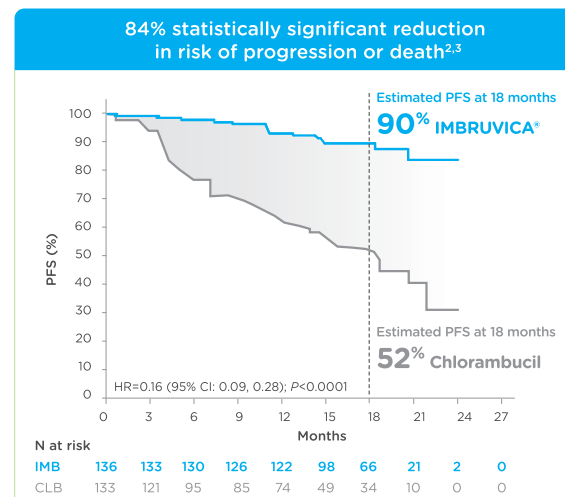
SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL



- Median follow-up was 28 months²
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm²

PROLONGED PROGRESSION-FREE SURVIVAL^{2,3}

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL



- Median follow-up was 18 months³
- With IMBRUVICA®, median PFS was not estimable vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil²
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria³

RESONATE™-2 Adverse Reactions ≥15%

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

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

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, neutropenia (58%)*, diarrhea (42%), anemia (39%)*, rash (31%), musculoskeletal pain (31%), bruising (31%), nausea (28%), fatigue (27%), hemorrhage (23%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (36%)*, thrombocytopenia (15%)*, and pneumonia (10%).

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

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

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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

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

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib)

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

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to IMBRUVICA in clinical trials. [see *Adverse Reactions*]. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

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

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

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

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

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

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

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

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

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

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

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

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

* Includes multiple ADR terms

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

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

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

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

<1 used for frequency above 0 and below 0.5%

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

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

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

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

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

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

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

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

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.
Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 12 and 13 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

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

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

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

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

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

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

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

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

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

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

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

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

* Includes multiple ADR terms.

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

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

Additional Important Adverse Reactions: Cardiac Arrhythmias: In randomized controlled trials (n=1377; median treatment duration of 14.0 months for patients treated with IMBRUVICA and 7.5 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 8% versus 2% and for Grade 3 or greater was 4% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: Diarrhea of any grade occurred at a rate of 40% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range: 0 to 475) versus 47 days (range: 0 to 492) for any grade diarrhea and 77 days (range: 3 to 310) versus 194 days (range: 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 84% versus 88% had complete resolution, and 16% versus 12% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 6 days (range: 1 to 655) versus 5 days (range: 1 to 367) for any grade diarrhea and 6 days (range: 1 to 78) versus 19 days (range: 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 12% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 96 days (range, 0 to 617) versus 109 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 61% versus 71% had complete resolution and 39% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 31 days (range, 1 to 457) versus 29 days (range, 1 to 253) in IMBRUVICA-treated subjects compared to the control arm, respectively.

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

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

DRUG INTERACTIONS

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

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

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 sternbrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

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

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

Females and Males of Reproductive Potential: Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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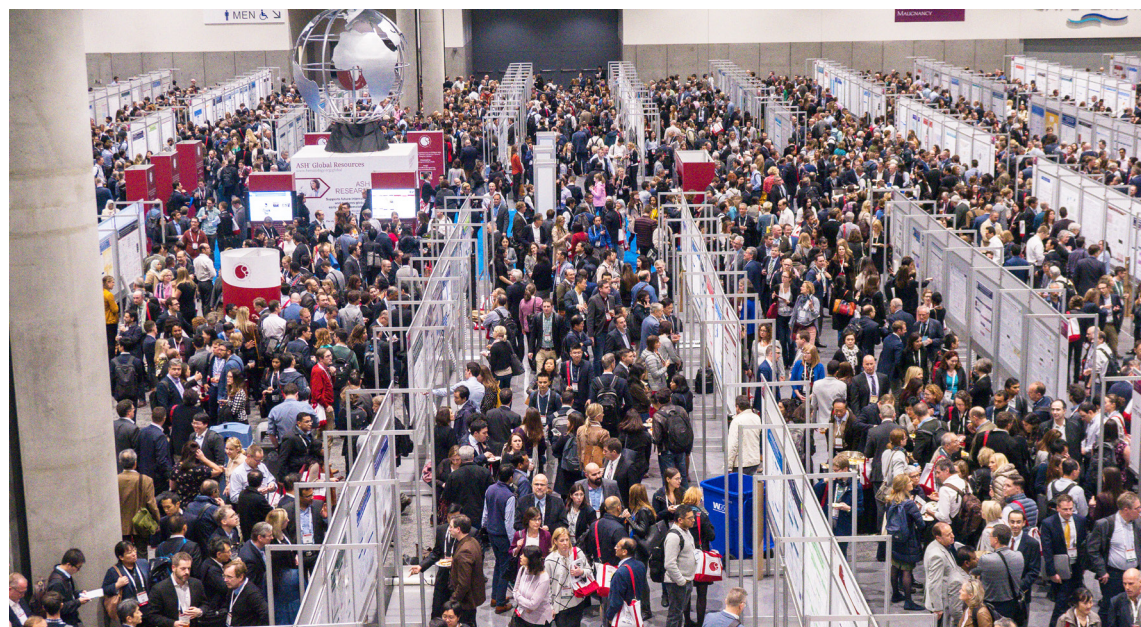
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PRC-04483

SPECIAL ISSUE / ASH MEETING RECAP
JANUARY 2019
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The ASH annual meeting brings more than 25,000 people to its host city.

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FROM THE CHAIRMAN

Bringing CAR T-Cell Therapy Into the Real World

THE 2018 MEETING OF the American Society of Hematology (ASH) brought reports from the front-lines about chimeric antigen receptor (CAR) T-cell therapy, which has captured the attention of the cancer treatment world, given the responses seen in certain leukemias and lymphomas. However, there are always new findings once novel treatments are approved and move beyond clinical trials into the real-world setting. In this special issue with reports from the ASH meeting in San Diego, California, we hear what happened when patients outside clinical trials were administered CAR T-cell therapy.

What did we learn? Caron A. Jackson, MD, of Dana-Farber Cancer Institute, tells us that in the real world, the eligibility criteria may not look like that of a clinical trial and some patients may need “bridging therapy” between leukapheresis, when their blood cells are removed, and treatment with the CAR T product.

We learn from Tanya Siddiqi, MD, of City of Hope, that one of the biggest variables in the overall cost of treatment is how long a patient stays in the hospital. A patient in her study that evaluated the cost of administering lisocabtagene maraleucel (liso-cel), which could become the third approved CAR T-cell therapy, was hospitalized for 34 days due to grade 4 cytokine release syndrome, at a cost above \$200,000.

But scientists are also learning ways to limit adverse events. Another study presented at ASH showed that receiving ibrutinib throughout CAR T-cell treatment reduced toxicity for many patients.

The other toxicity that remains is more financial. As 2018 came to a close, Joseph A. Alvarnas, MD, the hematologist/oncologist and editor-in-chief of *Evidence-Based Oncology*TM who serves as vice president of government affairs and senior medical director for employer strategy at City of Hope, warned that academic medical centers still lack guidance from CMS on reimbursement for CAR T-cell therapy. As a result, published reports say that some institutions are not providing the treatment. FDA Commissioner Scott Gottlieb, MD, who serves in the same department as CMS, is on the record warning that the reimbursement logjam could harm innovation.¹

As we hear that institutions are moving ahead with studies of CAR T-cell therapy in solid tumors, the challenge of reimbursement begs to be resolved. Perhaps this is one issue on which members of both parties in the new divided Congress can agree. ♦

REFERENCE

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Sincerely,

Mike Hennessy, Sr
 CHAIRMAN AND CEO

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Meeting attendees visit the on-site ASH store.

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Real-World Evidence With Axicabtagene Ciloleucel CAR T-Cell Treatment Similar to ZUMA-1 Trial Findings

Surabhi Dangi-Garimella, PhD

A MULTICENTER RETROSPECTIVE STUDY that evaluated the efficacy and safety of chimeric antigen receptor (CAR) T-cell treatment, axicabtagene ciloleucel (axi-cel; Yescarta), in a real-world setting produced a similar response as well as toxicity compared with the ZUMA-1 clinical trial results. Predictors of response included low day 0 C-reactive protein (CRP) and high absolute lymphocyte count at leukapheresis. The results were presented December 1, 2018, during the 60th American Society of Hematology (ASH) Annual Meeting & Exposition, held in San Diego, California.¹

The FDA approved axi-cel in October 2017,² and long-term results for the treatment were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in June 2018.³ The results presented at ASCO showed the objective response rate (ORR) was 82% at 8.7 months, which had been maintained by the long-term 15.4-months follow-up time. The complete response (CR) rate was 58% at the long-term follow-up.

Caron A. Jacobson, MD, instructor in medicine, Department of Medical Oncology, Dana-Farber Cancer Institute, and first author of the study presented at ASH, said that in a real-world setting, eligibility criteria and patient management factors may be very distinct from a clinical trial setting. Therefore, bridging therapy may be needed between leukapheresis and treatment with the CAR T product.

Thus, the study examined patient and disease characteristics and biomarkers of response or toxicity following axi-cel treatment in a real-world setting. In this case, the settings were 6 US academic medical centers that used commercial axi-cel.

Among the 104 patients with lymphoma who were part of this retrospective study (median age was 63.8 years; range, 21-80), 94 (90%) had an European Cooperative Oncology Group (ECOG) performance status of 0-1 and 48 (46%) had a prelymphodepletion International Prognostic Index (IPI) score of ≥ 3 . Twenty-eight (27%) patients had a prior autologous transplant and 3 (3%) had received a prior allogeneic stem cell transplant. Forty-two patients (40%) each had bulky disease (tumor bulk >5 cm) and received bridging therapy following leukapheresis.

At a median follow-up of 5.6 months, 13 patients had their T cells collected but they did not receive CAR T-cell infusion: 6 patients had progressive disease, 2 patients had infections, 3 patients had technical issues with cell production, 1 patient had a CR to bridging therapy, and 1 patient had another malignancy diagnosed.

When evaluated in 95 patients, an overall response (OR) was observed in 67 (62%) patients. A CR was observed in 42 (44%) patients and a partial response (PR) in 25 (26%). Among 51 patients with a 6-month follow-up, an OR was observed in 22 (43%).

Half of the patients who had an initial PR and who were not being followed went on to have a CR, Jacobson said. The median duration of response was 4.9 months.

According to Jacobson, univariate analysis showed that ECOG performance status ($P = .009$), tumor bulk ($P = .016$), baseline CRP ($P = .029$), and prior ibrutinib (Imbruvica) treatment ($P = .002$) had a significant association with lack of response to treatment with axi-cel.

Toxicity

A majority (96%) of the treated patients experienced cytokine-release syndrome (CRS), a flare-up that is characterized by low/high fever and low blood pressure and can sometimes lead to

capillary leak syndrome, according to Stephen J. Schuster, MD, of the Perelman School of Medicine.⁴

In 17 (16%) patients, CRS was grade 3 or higher; 2 patients (2%) died. A median time to onset was 1 day (range, 0-14), symptoms associated with the flare-up lasted a median of 6 days (range, 1-27). Fifty-eight (55.7%) patients experienced neurotoxicity following treatment with axi-cel, 29 (50%) of whom had grade 3 or higher neurotoxicity. There was 1 fatality associated with this toxic effect. Neurotoxic effects had a median onset time of 5 days (range, 0-34) and lasted for a median of 8 days (range, 1-52 days). Patients received tocilizumab (Actemra; $n = 70$) and steroids ($n = 66$) to counter the toxicity, and 30% required a stay in an intensive care unit. Six patients died following disease progression, and 5 died from toxicity. Univariate analysis that the researchers conducted for toxicity, mainly grade 3 or higher CRS or neurotoxicity, found no association with performance status, tumor bulk, IPI, prior treatment, bridging therapy, or eligibility for ZUMA-1.

Cytogenetic and immunohistochemistry staining found that 3 patients with programmed death ligand -1 positive (PD-L1) tumors were refractory to CAR T-cell therapy. Based on the staining results, a positive response could be associated with increased expression of PD-1, 41BB, ICOS, and Ki67, as well as CC3 indicating apoptosis, when CAR T-cell levels peaked by day 7. Subsequently, CAR T cells fell by day 14.

Jacobson said that the deviation from the observations in the ZUMA-1 trial may be due to the inclusion of sicker patients with a poorer performance status and possible different histologies in this patient population. Although rates of CRS and neurotoxicity were similar to ZUMA-1, toxicity was not associated with tumor bulk or response, but with higher peak inflammatory markers and absolute lymphocyte count, indicative of peak CAR T-cell levels.

"Unique combination approaches are necessary for specific patients/tumors," she noted, adding that their trial results support the use of axi-cel outside of strict clinical trial criteria, although the outcomes may be slightly inferior. ♦

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JACOBSON

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Ibrutinib Alone Better Than Chemoimmunotherapy as Frontline in Older Patients With CLL

Surabhi Dangi-Garimella, PhD



WOYACH

Jennifer A. Woyach, MD, associate professor, The Ohio State University College of Medicine, Columbus

ACCORDING TO THE RESULTS of Alliance A041202, an international multicenter phase 3 trial, ibrutinib (Imbruvica) produces superior progression-free survival (PFS) compared with standard chemoimmunotherapy (CIT) in older patients with chronic lymphocytic leukemia (CLL), and adding rituximab (Rituxan) does not improve the ibrutinib response.¹ The results were presented as part of the plenary session on December 2, 2018, at the 60th American Society of Hematology (ASH) Annual Meeting & Exposition in San Diego, California.

Accounting for about 25% to 30% of US leukemia cases, the American Cancer Society reports that nearly 21,000 new cases of CLL were diagnosed last year and the disease was responsible for about 4500 deaths.²

CIT has been the gold standard for patients, with bendamustine plus rituximab (BR) being a standard, more aggressive CIT regimen for patients age 65 or older. The Bruton tyrosine kinase inhibitor ibrutinib was approved by the FDA in 2016 for CLL,³ but it's only been compared with chlorambucil in this patient population, not with aggressive CIT. Also, the impact of adding rituximab to the ibrutinib treatment has not been evaluated, explained Jennifer A. Woyach, MD, associate professor, The Ohio State University College of Medicine, Columbus.

"Older patients are underrepresented in CLL clinical trials, unless the trial has been specifically designed for them," Woyach said.

Data from the RESONATE-2 trial presented at the 2017 ASH annual meeting compared treatment-naïve patients receiving ibrutinib as a single agent or chemoimmunotherapy regimens with patients with CLL who were receiving various combination treatments. Based on their results, the authors recommended that single-agent ibrutinib could be used in place of the combination chemotherapy regimens.⁴

The Alliance A041202 trial has 3 treatment arms—BR (arm 1), ibrutinib alone (arm 2), and ibrutinib plus rituximab (arm 3)—which are designed to determine whether ibrutinib-containing regimens lead to superior PFS compared with CIT in treatment-naïve older patients.⁵ PFS was defined as the time from randomization to first detection of disease progression or death. Additionally, this study sought to determine if adding rituximab to ibrutinib would prolong PFS over ibrutinib alone, Woyach said. The trial design allowed patients on arm 1 who progressed to cross over to arm 2. Data for the presentation at the ASH meeting were locked on October 4, 2018, Woyach added.

For trial inclusion, patients had to be 65 years or older with previously untreated, symptomatic CLL; creatinine clearance had to be at least 40 mL/min; bilirubin had to be ≤ 1.5 the upper limit of normal; and patients should have had no significant life-limiting intercurrent illness or need for warfarin treatment. Of the 644 patients who were screened, 547 were randomized 1:1:1 to the 3 arms. Thirty patients in the BR arm crossed over to the ibrutinib-alone arm following analysis.

The median age of trial enrollees was 71 years (range, 65-89) and a majority (67%) were men. High-risk Rai stage (stage III/IV) was detected in 54% of patients, unmethylated Zap-70 in 53%, del(17p) or del(11q) by local fluorescence in situ hybridization analysis in 25%, and complex karyotype in 29%.

PFS was higher in the ibrutinib-alone cohort compared with the ibrutinib-plus-rituximab cohort, Woyach said. In the eligible patient population, at a median follow-up of 24 months, 74% of patients in arm 1 were alive and progression-free (95% CI, 66%-80%) compared with 87% in arm 2 (95% CI, 81%-92%) and 88% in arm 3 (95% CI, 81%-92%).

No significant differences in PFS were observed in the 2 ibrutinib arms among patients with a complex karyotype, she said. Two-year PFS estimates were 59%, 39%, and 87% in arms 1, 2, and 3, respectively. Overall response rates in the intent-to-treat population were 81%, 93%, and 94%, respectively, and the complete response rates were 26%, 7%, and 12%.

"We did not observe any significant differences in overall survival [OS] among the arms, which might be due to the crossover or the short follow-up time," Woyach said. She reported that median OS had not been reached for any arm, and OS estimates were 95%, 90%, and 94% for arms 1, 2, and 3, respectively, at a 38-months follow-up.

Adverse events (AEs) were observed at a significantly high rate in this trial. Hematologic AEs were observed in 61%, 41%, and 38% of patients in arms 1, 2, and 3, respectively. Nonhematologic AEs were observed in 63%, 74%, and 74%.

"Hematologic AEs were prevalent in the BR arm while nonhematologic AEs were more common in the ibrutinib arms," Woyach said. "Unexplained or unwitnessed death over the entire observation period was seen in 2 [1.1%], 7 [3.9%], and 13 [7%] patients in arms 1, 2, and 3 respectively."

Concluding her presentation, Woyach said that the findings from their trial justify using ibrutinib as a standard-of-care treatment for patients 65 and older and that combining it with rituximab does not improve PFS outcomes. "Clinical trials of this patient population are still of high clinical interest, and the cooperative group setting remains a reasonable avenue to complete these large studies," she added. ♦

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Chemotherapy for Solid Tumors Associated With Increased Risk of AML, MDS
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iLLUMINATE: Superior PFS With Ibrutinib–Obinutuzumab Even in High-Risk, Untreated CLL/SLL

Surabhi Dangi-Garimella, PhD

IBRUTINIB COMBINED WITH obinutuzumab had better progression-free survival (PFS) at 30 months than the standard chemotherapy regimen, chlorambucil plus obinutuzumab, regardless of high-risk genomic features in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) who had never been treated.¹ Carol Moreno, MD, presented results from iLLUMINATE December 3, 2018, at the 60th American Society of Hematology Annual Meeting & Exposition, held in San Diego, California.

Ibrutinib is a first-in-class, once-daily inhibitor of Bruton tyrosine kinase and was approved in 2016² in the United States as a single-agent, chemotherapy-free regimen for patients with CLL. The iLLUMINATE trial is a phase 3, open-label, multicenter trial that was designed to test the efficacy of ibrutinib with obinutuzumab versus chlorambucil with obinutuzumab in treatment-naïve patients with CLL and SLL.³ Eligibility criteria included treatment-naïve CLL/SLL and ≥65 years or <65 years with coexisting conditions (Cumulative Illness Rating Scale score >6, creatinine clearance <70 mL/min, and/or del(17p) or TP53 mutation).

Based on their findings, the authors conclude that the ibrutinib–obinutuzumab combination therapy was tolerable among treatment-naïve patients with chronic lymphocytic leukemia or small lymphocytic leukemia.

One set of patients received 6 cycles of 420-mg ibrutinib once daily, combined with obinutuzumab 1000 mg on days 1/ 2, 8, and 15 of cycle 1, and day 1 of subsequent 28-day cycles. The other set of patients was treated with 6 cycles of chlorambucil, which was 0.5 mg/kg on days 1 and 15 of each 28-day cycle, combined with obinutuzumab, in the same dose and frequency as above. PFS was the primary endpoint, and secondary endpoints included PFS in a high-risk population—del(17p)/TP53 mutation, del(11q), and/or unmutated *IGHV*—rate of undetectable minimal residual disease, overall response rate (ORR), overall survival (OS), and safety. The trial allowed crossover of patients with confirmed progression in the chlorambucil–obinutuzumab arm to single-agent ibrutinib.

The trial enrolled 229 patients, 113 of whom were randomized to the ibrutinib–obinutuzumab arm and 116 to the chlorambucil–obinutuzumab arm. Median age was 71 years (range, 40–87) and 65% of patients had the above listed high-risk genomic features.

With a median follow-up of 31.3 months, patients who were treated with ibrutinib–obinutuzumab had a significantly better PFS compared with the comparator arm (median not reached [NR] vs 19.0 months; HR, 0.231; 95% CI, 0.145–0.367; $P < .0001$). At 30 months, the PFS rates were 79% with ibrutinib–obinutuzumab and 31% with chlorambucil–obinutuzumab. These were PFS results as assessed by an independent review committee (IRC), the authors reported.

Investigator (INV)-assessed PFS showed a similar trend for ibrutinib–obinutuzumab versus chlorambucil–obinutuzumab

(median PFS NR vs 21.9 months; HR, 0.260; 95% CI, 0.163–0.415; $P < .0001$). Further, the improvements in PFS seen among patients receiving ibrutinib–obinutuzumab were independent of their genomic status compared with the comparator arm (median NR vs 14.7 months; HR, 0.154; 95% CI, 0.087–0.270; $P < .0001$).

Both IRC- and INV-assessed ORR were better for the ibrutinib–obinutuzumab arm. IRC-assessed ORR was 88% with ibrutinib and obinutuzumab versus 73% with the comparator, and INV-assessed ORRs were 91% and 81%, respectively. Similar trends were observed with the IRC-assessed complete response (CR) rate, which was higher with ibrutinib and obinutuzumab (19% vs 8%). INV-assessed CR rates were 41% and 16%, respectively.

The authors report similar 30-month OS rates: 86% in the ibrutinib–obinutuzumab arm and 85% in the chlorambucil and obinutuzumab arm, with 40% of patients randomized to chlorambucil–obinutuzumab receiving single-agent ibrutinib as second-line therapy. Over a median follow-up of 31.3 months, 4% of patients in the ibrutinib–obinutuzumab arm and 44% in the chlorambucil–obinutuzumab arm initiated subsequent therapy.

Adverse Events

The most frequent (≥3%) serious adverse events (AEs) among patients in the ibrutinib–obinutuzumab arm were pneumonia (5%), atrial fibrillation (4%), febrile neutropenia (4%), and pyrexia (4%). The more common serious AEs in the chlorambucil–obinutuzumab were infusion-related reactions (IRRs; 7%), febrile neutropenia (6%), pneumonia (4%), tumor lysis syndrome (4%), and pyrexia (3%). Although no patients discontinued obinutuzumab due to IRRs in the ibrutinib and obinutuzumab arm, 7 patients in the comparator stopped obinutuzumab.

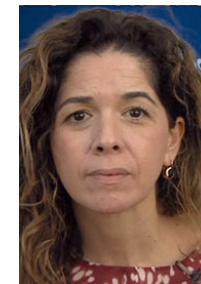
AEs leading to discontinuation of ibrutinib and chlorambucil occurred in 18 (16%) and 11 patients (9%), respectively, and AEs leading to discontinuation of obinutuzumab occurred in 10 patients (9%) in the ibrutinib–obinutuzumab arm and 15 (13%) in the chlorambucil–obinutuzumab arm.

At about the 3-year follow-up mark, 70% of patients in the ibrutinib–obinutuzumab arm were on single-agent ibrutinib.

Based on their findings, the authors concluded that the ibrutinib–obinutuzumab combination therapy was tolerable among treatment-naïve patients with CLL/SLL, with no new safety signals identified, and that it represents an effective chemotherapy-free treatment option for first-line CLL/SLL, including among the high-risk population. ♦

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ELOQUENT-3: Adding Elotuzumab to Pomalidomide, Dexamethasone Improves PFS in R/R Multiple Myeloma

David Bai, PharmD



DIMOPOULOS

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ELOQUENT-3 TRIAL RESULTS show that adding elotuzumab to pomalidomide and dexamethasone improved progression-free survival (PFS) and overall response rate (ORR) in patients with multiple myeloma who had relapsed from or were refractory to (R/R) lenalidomide and a proteasome inhibitor. Results were presented December 1, 2018, at the 60th American Society of Hematology Annual Meeting & Exposition and previewed in the *New England Journal of Medicine*.¹

Immunomodulatory agents and proteasome inhibitors are the mainstay for treatment of multiple myeloma. Once patients relapse or become refractory, prognosis becomes extremely poor, with overall survival averaging 9 months. The triplet regimen of elotuzumab in combination with lenalidomide and dexamethasone, which combines an immunomodulatory agent with elotuzumab in patients with multiple myeloma who have progressed after at least 1 previous therapy, was approved in 2015.²

Elotuzumab is a humanized monoclonal antibody that binds to signaling lymphocytic activation molecule F7 (SLAMF7) on the surface of myeloma cells and natural killer cells to initiate natural killer cell-mediated cellular cytotoxicity or macrophage-mediated killing on myeloma cells. Because pomalidomide also affects the immune system, investigators said that a combination of elotuzumab and pomalidomide will work synergistically and enhance cell-mediated killing of myeloma cells. In the phase 2 ELOQUENT-3 study, the efficacy and safety of elotuzumab plus pomalidomide and dexamethasone were compared with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma who had already received lenalidomide and a proteasome inhibitor.

Patients who were relapsed/refractory to lenalidomide and a proteasome inhibitor were randomized in a 1:1 ratio to receive either elotuzumab plus pomalidomide and dexamethasone

(elotuzumab group) or pomalidomide and dexamethasone (control group). Median PFS was 10.3 months in the elotuzumab group compared with 4.7 months in the control group (HR, 0.54; 95% CI, 0.34-0.86; $P = .008$). The addition of elotuzumab was beneficial across all key patient subgroups, including patients who had received at least 4 previous lines of therapy and patients with at least 1 cytogenetic abnormality (eg, chromosome 17p deletion). ORR was also higher in the elotuzumab group (53%) than in the control group (26%), with 20% of patients in the elotuzumab group having a very good partial response or better compared with 9% in the control group. Median duration of response was not reached in the elotuzumab group; it was 8.3 months in the control group.

Reported adverse events (AEs) were similar between the 2 groups. The most common grade 3-4 AEs in the elotuzumab group and control group, respectively, were neutropenia (13% vs 27%), anemia (10% vs 20%), infections (13% vs 22%), and hyperglycemia (8% vs 7%). AEs that led to discontinuation occurred in 18% of the patients in the elotuzumab group compared with 24% of the patients in the control group.

Elotuzumab in combination with pomalidomide and dexamethasone was shown to be effective and safe and can be considered for patients who have progressed after lenalidomide and a proteasome inhibitor. ♦

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Carfilzomib-Based Combination Results in Sustained MRD-Negative Complete Response in Multiple Myeloma

Jaime Rosenberg

UPFRONT TREATMENT WITH CARFILZOMIB, lenalidomide (Revlimid), and dexamethasone (KRd) with lenalidomide maintenance incorporating a “by-default-delayed” autologous stem cell transplant (ASCT) strategy in newly diagnosed multiple myeloma has demonstrated high rates of minimal residual disease negativity (MRD negative) complete response (CR).

Expanding on these results, researchers at the 60th American Society of Hematology Annual Meeting & Exposition, held December 1-4, 2018, in San Diego, California, presented long-term study results showing that these responses were sustained with a median duration of over 4 years among treatment-naïve patients with multiple myeloma.

The 45 patients in the phase 2 study were treated for 8 cycles (28-day cycles) with carfilzomib 20/36 mg/m² intravenously on days 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg orally days 1-21; and dexamethasone 20/10 mg intravenously/orally days 1, 2, 8, 9, 15, 16, 22, and 23. Patients who were transplant-eligible underwent stem cell collection after 4 or more cycles and then continued KRd treatment.

MULTIPLE MYELOMA / MYELOFIBROSIS

Following 8 cycles of KRd, patients received 2 years of lenalidomide 10 mg oral maintenance on days 1-21.

The primary objective of the study was to assess the rate of grade ≥ 3 peripheral neuropathy with secondary objectives of overall response rate (ORR), MRD negative CR, time to progression, and response duration assessed after every cycle during induction and subsequently after every 90 days of maintenance therapy. MRDneg CR was assessed by multi-color flow cytometry after 8 cycles of induction, 1 and 2 years of lenalidomide, and then annually.

Median potential follow-up was 5.7 years. The ORR was 97.8% (95% CI, 88.2%-99.9%) with a median duration of response of 65.7 months (95% CI, 55.6-not reached months). Notably, 28 patients (62.2%) had deep responses of MRD negative CR, and the durability was observed up to at least 70 months with a median duration of over 4 years.

Median time to progression was more than 5.5 years and median overall survival was not reached. However, at 80 months, 84.3% of patients were still alive. "As expected, patients who attained MRDneg CR by cycle 8 had a 78% reduction in the risk of progression," wrote the researchers.

They added that these deep responses of MRD negative CR and long progression-free durations occurred regardless of age or cytogenetic-based risk profile. Toxicities were generally manageable with no grade ≥ 3 neuropathy or death due to toxicity. ♦

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CLINICAL / MYELOFIBROSIS

Ruxolitinib Results in Better Treatment Response, Less Toxicity in Early Primary Myelofibrosis

Jaime Rosenberg

FOR THE FIRST TIME, a study has demonstrated that early primary myelofibrosis (PMF) represents a category of patients who are likely to have better responses and lower toxicities from treatment with ruxolitinib. According to the study, led by Francesca Palandri, MD, PhD, of the Institute of Hematology at the University of Bologna, Italy, presented at the 60th American Society of Hematology Annual Meeting & Exposition, held December 1-4, 2018, in San Diego, California, a World Health Organization (WHO)-defined diagnosis may help better identify patients who may need strict monitoring during treatment with ruxolitinib (Jakafi).

In 2016, WHO criteria labeled early PMF as an individual entity with different clinical and laboratory presentations, as well as a significantly better outcome compared with overt PMF. However, there is a lack of information on the therapeutic effects of ruxolitinib depending on treatment setting.

Aiming to provide data on the differences in baseline clinical and laboratory characteristics, response to treatment, and toxicity between early and overt PMF treated with ruxolitinib, researchers utilized a clinical database in 23 European hematology centers. The database included retrospective data of 537 patients with myelofibrosis (MF) treated with ruxolitinib between January 2011 and July 2018. Spleen and symptom response were documented, and hematologic toxicity and infections were graded.

Of the 199 patients, 59 had a diagnosis of early PMF and 140 had a diagnosis of overt PMF. Median time from diagnosis to ruxolitinib initiation was 22.4 months.

Compared with patients with overt PMF, patients with early PMF started ruxolitinib with higher hemoglobin levels (median, 11.6 vs 10.4 g/dL) and lower circulating blast counts. They were also more frequently at intermediate-1 Dynamic International Prognostic Scoring System risk (69.6% vs 42.5%). The ruxolitinib starting doses and 12-week titrated doses were comparable between the 2 groups.

At 3 months, 43.1% of patients with early PMF achieved a spleen response, and at 6 months 48.9% achieved a spleen response, compared with 27.9% and 31.3% of patients with overt MF

respectively. The rate of symptom response was also higher among patients with early PMF at both 3 months (82.5% vs 68.8%) and 6 months (90.0% vs 73.7%).

Toxicities and infections also favored patients with early PMF. In the first 12 months from ruxolitinib initiation, anemia and thrombocytopenia of all grades were observed in 75.6% and 43.1% in patients with overt PMF and in 86.3% and 60.0% of patients, respectively, with early PMF.

In 2016, the World Health Organization criteria labeled early PMF as an individual entity with different clinical and laboratory presentations, as well as a significantly better outcome compared with overt PMF.

At 3 months, anemia was more prevalent among patients with overt PMF (94.7% vs 80.0%), with 32.6% of these patients having grade 3-4 anemia compared with 17.8% in early PMF. Similarly, rates of thrombocytopenia were also higher among patients with overt PMF at 3 months (51.5% vs 36.2%) and at 6 months (52.9% vs 35.8%), with only 2.2% and 2.5% of patients having grade 3-4 thrombocytopenia, respectively.

During treatment, 75 patients had at least one grade 2 or greater infectious episode. Overall, 108 patients discontinued treatment (52.5% of patients with early PMF and 55% of patients with overt PMF). Evolution into acute leukemia occurred in 21 patients.

Overall survival and progression-free survival were comparable between the 2 groups. ♦

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PALANDRI

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Myelofibrosis Survival After Discontinuing Ruxolitinib Differs Based on Reason for Discontinuation

Jaime Rosenberg

RUXOLITINIB (JAKAFI) IS THE ONLY targeted therapy available for the treatment of myelofibrosis (MF)-related splenomegaly and symptoms, and although 50% of patients with MF achieve significant clinical responses with ruxolitinib, half the responders stop responding over time.

Following failure with ruxolitinib, there are limited treatment options available. Among patients who fail on the treatment, prognosis is unfavorable, particularly among those who started ruxolitinib with advanced-stage disease, according to study results presented at the 60th American Society of Hematology Annual Meeting & Exposition held in San Diego, California.

The results further indicated that discontinuation because of disease evolution into acute leukemia or because of occurrence of a second solid neoplasia significantly reduced life expectancy.

The researchers assessed retrospective data from a clinical database created in 23 European hematology centers. The data included information on 537 patients treated with ruxolitinib from January 2011 to July 2018; information on 442 patients available as of July 15, 2018, was reported.

Spleen and symptom response to treatment were evaluated, and ruxolitinib-related toxicity and infections were graded. Overall survival was estimated

from the date of ruxolitinib discontinuation to the date of death or last contact.

After a median follow-up of 30.5 months, 214 of the 442 (48.4%) evaluable patients discontinued ruxolitinib. Among these patients, (20.1%) died while on therapy because of MF progression (34.9%), infection (25.6%), heart disease (16.3%), second neoplasia (7%), hemorrhages (7%), and other causes (9.2%). Among the remaining 171 patients who discontinued ruxolitinib, median follow-up was 11.3 months. Reasons for discontinuation included drug-related toxicity (28.6%), loss or lack of response (23.4%), MF progression (12.3%), acute leukemia (13.4%), allogeneic stem cell transplantation (ASCT) (11.1%), second solid neoplasia (4.1%), and other unrelated causes (7.1%).

After discontinuing ruxolitinib, 68 patients received 1 line of therapy, 21 received 2 lines, and 9 received more than 2 treatments. Additionally, 73 patients did not receive any therapy. Treatments received after ruxolitinib discontinuation, alone or in combination, included hydroxyurea, ASCT, second-generation *JAK2* inhibitors, splenectomy, azacytidine/decitabine, chemotherapy, investigational agents, danazole, and erythropoietin-stimulating agents.

A total of 95 patients died following ruxolitinib discontinuation due to MF progression (30.5%),

acute leukemia (25.4%), infections (14.7%), second neoplasia (9.5%), hemorrhages (4.2%), heart disease (4.2%), ASCT (4.2%), thrombosis (2.1%), and other causes (5.2%). Median survival time following ruxolitinib among the 171 patients was 22.6 months.

Survival following discontinuation was significantly influenced by Dynamic International Prognostic score category, transfusion dependency, and driver mutation status at baseline.

While receiving therapy, 45 of 153 (29.4%) and 123 of 161 (76.4%) evaluable patients achieved a spleen and symptoms response at any point, but survival was not affected by the previous response to treatment. However, survival significantly varied based on the reason for stopping treatment, with those discontinuing because of acute leukemia evolution or second solid neoplasia having the worst outcome.

Among patients who discontinued treatment in chronic phase, the use of second-generation tyrosine kinase inhibitors and other investigational agents prolonged survival compared with administration of conventional treatments. ♦

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CLINICAL / LYMPHOMA

CT-P10 Is Similar to Reference Rituximab in Previously Untreated Advanced Follicular Lymphoma

Samantha DiGrande

AT THE 60TH AMERICAN SOCIETY of Hematology's Annual Meeting & Exposition in San Diego, California, held December 1-4, 2018, researchers presented data from an ongoing randomized, double-blind trial comparing the efficacy of CT-P10 (Truxima)—a newly approved rituximab biosimilar—with reference rituximab (Rituxan) in patients with previously untreated advanced follicular lymphoma.

The study enrolled 140 patients, 124 patients of whom completed the full 8 cycles of rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) induction therapy.¹ In total, 122 patients

who showed response during the induction period (62 patients in the CT-P10 treatment arm and 60 patients in the reference arm) then moved on to the maintenance period, during which 12 cycles of rituximab monotherapy were administered at intervals of 2 months.

Efficacy was determined based on outcomes including progression-free survival, duration of response, and overall survival (OS). The updated safety profile of CT-P10 compared with reference rituximab in advanced follicular lymphoma was also assessed. The study was designed to continue until

death or up to 3 years from the randomized date of the last patient.

At the time of the cutoff date, the median follow-up was 23 months (range, 0.5-34) in the CT-P10 group and 22 months (range, 0.2-33) in the reference rituximab group. The rates of relapse, disease progression, or death from any cause were 22.9% and 24.3% for the CT-P10 and reference rituximab groups, respectively.

As for sustained response, the proportion of patients who showed relapse or disease progression after previously achieving overall response was

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19.4% in the CT-P10 arm and 21.3% in the reference arm. Notably, there was no statistically significant difference in OS between either group with a 2-year OS of 93.2% for CT-P10 patients and 95.3% in reference rituximab patients.

Furthermore, “The updated safety results did not reveal any new trends or new signals noted in the patients treated with CT-P10,” a Celltrion representative said in an email.

The study’s authors concluded that, at the median follow-up of 23 months, the data demonstrated comparable progression-free survival, sustained

response, and OS between both the biosimilar and the reference product.

FDA approved CT-P10 on November 28, 2018, under the brand name Truxima, though a launch date has yet to be disclosed.² “Celltrion and Teva Pharmaceutical Industries entered into an exclusive partnership in October 2016 to commercialize Truxima in the United States and Canada. Teva and Celltrion have reached a settlement agreement with Genentech, including entry terms. The terms and conditions of that agreement are confidential at this time,” noted Woosung Kee, CEO of Celltrion. ♦

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CLINICAL / LYMPHOMA

Longer-Term JULIET Results Confirm Sustained Response With Tisagenlecleucel in Relapsed/Refractory DLBCL

Surabhi Dangi-Garimella, PhD

A MEDIAN 19-MONTH follow-up of the JULIET trial—a single-arm, open-label, multicenter, global, pivotal phase 2 trial of the chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel directed against CD19-expressing B cells—has found a 40% complete response (CR) and a manageable safety profile in adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL).¹

Tisagenlecleucel (Kymriah) was FDA approved in May 2018 for the treatment of adult patients with R/R large B-cell lymphoma following at least 2 prior lines of therapy.

Conducted across 27 sites in 10 countries, the JULIET trial enrolled 167 patients with R/R DLBCL at the cutoff date of May 21, 2018, and 115 of them received an infusion of CD19-directed CAR T cells (dose range 0.1 x 10⁸ to 6 x 10⁸ cells). Eligibility criteria included at least 18 years of age; at least 2 lines of prior therapy, including an anti-CD20 antibody and an anthracycline; and were ineligible for or had failed autologous stem cell transplant (ASCT). Primary trial endpoint was overall response rate (ORR), as a sum total of the CR and partial response as assessed by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), and safety.

About 90% of infused patients received bridging therapy and 93% received lymphodepleting chemotherapy. Median time from infusion to data cutoff was 19.3 months. Median age was 56 years (range, 22-76 years); 23% were aged ≥65 years. At study entry, 77% of infused patients had stage III/IV disease; 55% and 43% had germinal center and activated B-cell molecular subtypes, respectively. More than half of the patients had received at least 3 prior lines of antineoplastic therapy (range,

1-6) and about the same number had undergone a prior ASCT.

Of the 99 patients who were evaluated who had at least 3 months of follow-up, ORR was 54% (95% CI, 43%-64%), with 40% CR. Further, ORR was consistent across prognostic subgroups that were evaluated, including prior ASCT, gender, age, and molecular subtype.

Median DOR was not reached at the time of data analysis, and DOR was not influenced by age or R/R status, the study found. No relapses were observed beyond 11 months after infusion. The median OS for all infused patients was 11.1 months (95% CI, 6.6 months-not evaluable [NE]) and was not reached for patients in CR (95% CI, 21 months-NE). The OS probability was 48% (95% CI, 38%-57%) at 12 months and 43% (95% CI, 33%-53%) at 18 months, and, similar to DOR, was not influenced by the patient’s age or R/R status.

“These findings are consistent with what we’ve shown in our single-site studies here at Penn, which is that the majority of patients who go into remission stay in remission,” said Stephen J. Schuster, MD, director of the Lymphoma Program at the Abramson Cancer Center of the University of Pennsylvania, who is the principle investigator for the JULIET trial.²

The authors compared the survival curves from their current study with those of the SCHOLAR-1 study³ and the CORAL study,⁴ and they found that patients enrolled in JULIET performed much better in terms of OS. The OS probability was about 30% and 25% for SCHOLAR-1 and CORAL at 12 months, respectively, and 25% and 20% at 24 months, respectively.

More than half (57%) of patients experienced cytokine release syndrome, 34% of which were grade 3/4. Prolonged (>28 days) cytopenias were observed

in 45% patients, 34% of which were high-grade (3/4); a majority (17%) of infections in 37% of patients were grade 3. Twenty percent of treated patients experienced neurological adverse events, including a single case of grade 2 cerebral edema, which was detected without a contrast computed tomography (CT) scan, which disappeared following a contrast CT scan after 24 hours.

The authors report that there were no treatment-related deaths following their last data presentation at the Congress of the European Hematology Association in June 2018.⁵ ♦

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Length of Hospital Stay Key Driver of Costs Associated With CRS Following CAR T-Cell Treatment

Surabhi Dangi-Garimella, PhD



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HEALTH RESOURCE UTILIZATION DATA gathered from the TRANSCEND-NHL 001 trial show that longer stays in the intensive care unit (ICU) have a significant impact on the cost of care due to cytokine release syndrome (CRS) following treatment with chimeric antigen receptor (CAR) T cells. Presenting the results of the study at the 60th American Society of Hematology Annual Meeting & Exposition, held December 1-4, in San Diego, California, was Tanya Siddiqi, MD, hematologist/oncologist with City of Hope, Duarte, California.¹

CRS is a significant adverse effect of CAR T treatment. According to David Porter, MD, of the University of Pennsylvania Health System, T cells that have been activated release cytokines that activate other immune cells; this in turn releases more cytokines into the bloodstream. Consequently, the patient can experience high fever, severe flu-like symptoms, and other complications. This potentially fatal syndrome may require use of vasopressors, medications to improve blood pressure, and patients may need to be cared for in an ICU, Porter told *The American Journal of Managed Care*[®] in an interview.²

Although symptoms may vary based on the type of CAR T-cell treatment being administered, the TRANSCEND-NHL 001 phase 1 study is evaluating lisocabtagene maraleucel (liso-cel), comprising CD19-directed 4-1BB CAR T cells, in adult patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, follicular lymphoma Grade 3B, and mantle cell lymphoma.³

“Resource use [in CRS management] may differ by product and remains to be evaluated,” Siddiqi said. “We have tried to estimate the cost of CRS management in relapsed/refractory DLBCL,” she said, adding that their analysis focused on dose-finding and dose-expansion cohorts from the trial.

Participants were infused with 1 or more cycles of liso-cel, which includes lymphodepletion followed by 1 or 2 doses of the CAR T-cell infusion. The trial has a follow-up period of 24 months following the first infusion.

The authors looked at the case report forms of patients who experienced CRS to evaluate the health resource utilization (HRU) associated with CRS management, which was assessed using a 2-step micro-costing method.⁴ “Data cut-off was May 4, 2018,” Siddiqi said. In the first step, she explained, they analyzed HRU for managing each event, including number of inpatient days, number of ICU days, procedures, and medications.

“HRU was included if it was within the protocol management guidelines,” she added. The analysis included HRU that occurred within the onset date and resolution date of a treatment-related adverse event. In the second step, cost was attributed to each HRU, which included diagnostic and laboratory testing; hospitalization, procedures, and office visits; and medication costs.

“Our methods were consistent with previous microcosting efforts in CAR T adverse event management conducted by the Institute for Clinical and Economic Review,” Siddiqi said.

Analyses were stratified by grade and by site of care (eg, inpatient or outpatient), where the CAR T-cell therapy was administered.

The researchers used the Lee criteria⁵ for grading CRS, which clustered a majority of patients in the current cohort in grade 1 and grade 2. Of the 38 (out of 102) patients treated in the dose-finding/dose-expansion portions of the trial who experienced CRS, 19 (19%) patients experienced grade 1 symptoms, 18 (18%) grade 2, and 1 patient had grade 4 CRS. Total HRU and cost varied based on CRS grades. A higher grade of CRS, not surprisingly, was

associated with a longer length of stay (LOS): The mean LOS for grades 1 and 2 were 4 and 7 days, respectively, for inpatient CAR T administration. One patient with grade 4 had a LOS of 34 days. Among those who received outpatient CAR T-cell treatment, the mean LOS was 2 days for grade 1 CRS and 6 days for grade 2 CRS. Patients in the inpatient setting had longer mean LOS compared with those in the outpatient setting. Although patients with grade 1 CRS did not need ICU admission, the mean ICU LOS for CRS grade 2 patients was 1 day, and 1 patient was in the ICU for 26 days.

Siddiqi highlighted that patients were successfully managed with conservative HRU compared with the trial’s recommended guidelines. Only half (9/18) who experienced grade 2 CRS were administered the recommended tocilizumab, she said.

The analyses found that hospitalization had the most impact on overall cost, which was much lower for patients who experienced grade 1 (\$11,226) and grade 2 (\$25,617) CRS. Hospitalization costs alone were \$10,813 and \$21,397, respectively. The lone patient with CRS grade 4 who had a 34-day LOS, 26 of which were spent in the ICU, incurred an estimated total cost of \$201,836.

“More so than diagnostics and drugs, hospitalization led to a tremendous cost burden,” Siddiqi said. The 1 outlier was her own patient, who came in with a large disease burden to start with, and he had CRS as well as neurotoxicity, which is another adverse effect of CAR T-cell treatment. He was on a ventilator as well.

Resource use not referenced in the guidelines was largely made up of medication use and resulted in minimal increases in total cost. These costs ranged from \$1698 (grade 1) to \$21,055 (grade 4).

Siddiqi highlighted certain limitations of the study, including that grade 3/4 events are not well represented in their cohort. Additionally, CRS definitions, management, and incidence vary across CAR T-cell therapies, and costs were derived from national averages and may not be generalizable across institutions.

She concluded that based on the analysis, hospital and ICU LOS seem to be key drivers of CRS management cost and are mainly associated with managing higher-grade CRS. Siddiqi noted, however, that although actual costs may vary between hospitals, CRS management guidelines, which vary across CAR T therapies, will significantly affect both HRU and associated cost differences.

“Improvement of CAR T-cell therapy complications may be achieved through efficient intervention strategies and product engineering,” to reduce the incidence and the grade of CRS, Siddiqi said. ♦

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COST OF CARE

Studies at ASH Evaluate Episodic ED Utilization, Adherence, QOL in Sickle Cell Disease

Surabhi Dangi-Garimella, PhD

PATIENTS WITH SICKLE CELL DISEASE (SCD) typically have episodic emergency department (ED) and inpatient encounters, and innovative interventions are necessary to improve adherence to hydroxyurea (HU) treatment among youth suffering from SCD. These were the findings of 2 studies presented during an outcomes research session December 1, 2018, at the 60th American Society of Hematology (ASH) Annual Meeting & Exposition, held in San Diego, California.

ED utilization and inpatient admission among patients with SCD are known issues, but utilization can vary among individual patients. A 30-month study that involved 427 patients in 2 institutions in North Carolina, for example, found that 1 cohort of patients with SCD had more hospital admissions and ED encounters while the other cohort had more day hospital encounters.¹ Pain associated with SCD is a common reason for ED visits.^{2,3}

Further research will include determining the likelihood of change in state for a given patient based on history and prior state. Additionally, the researchers plan to identify whether health events or patient characteristics are associated with occasional or high-use states.

The first study, presented at the ASH annual meeting by Susan Paulukonis, MA, MPH, program director, California Rare Disease Surveillance Program, evaluated both high-use and quiescent periods among patients seen in California's nonfederal hospitals over 12 years.⁴

"We were seeing peaks and valleys of ED utilization, and we wanted to understand those patterns better," Paulukonis said.

The data are part of the California Sickle Cell Data Collection project, a statewide effort to use a wide range of administrative, clinical, and other data sources to describe the population living with SCD, their health outcomes, and healthcare utilization patterns. Paulukonis shared analyses of data gathered from inpatient and ED encounters (with or without an associated inpatient stay) from 2005 to 2016. Patient identifiers across data set and year helped link the patient information. A true SCD case was defined as 3 or more occurrences of a SCD-specific *International Classification of Diseases* code (version 9 or 10) within any 5-year period between 2005 and 2016. Patients who met this definition and had at least a 1-year follow-up were included in the analyses.

Quiescent periods were defined as lengths of time in which a person had zero or near-zero encounters in ED or inpatient settings. Occasional and high-use periods of ED utilization were quantitatively defined by the model.

"Among the 5090 patients who qualified for the study, the median follow-up period was 9.8 years, with a range of 1.0 to 11.0 years. There were over 94,000 stand-alone ED encounters, while over 59,000 ED encounters were associated with an inpatient stay," Paulukonis said when describing the cohort that was analyzed.

A 3-component model was used to combine predictive power, parsimony, and clinical relevance, including quiescent periods (mean, 0.09 encounters; 88.8% of 4-week periods), occasional-use

periods (mean, 1.28 encounters; 10.8% of 4-week periods), and high-use periods (mean, 7.48 encounters; 0.5% of 4-week periods).

All but 2 patients experienced at least 1 quiescent period during the study period, 75.9% experienced at least 1 occasional-use period, and 8.0% experienced at least 1 high-use period. According to Paulukonis, patient age did not influence the occasional- or high-use periods, which lasted a median of 8 weeks; 3.6% of these spells included at least some very high-use. Younger patients (<20 years) had longer durations of quiescent periods compared with older (≥ 20 years) patients (median, 24 vs 16 weeks, respectively).

Paulukonis concluded that most patients with SCD experience discrete periods during which ED and inpatient hospital encounters are not uncommon, separated by somewhat longer periods with few encounters or none. Additionally, younger patients are more likely to experience these high-frequency episodes. "We will try to tease out if, based on a patient's status at a particular time, what will happen to the patient 2, 4, or 6 months from that time," Paulukonis said.

Further research will include determining the likelihood of change in state for a given patient based on history and prior state. Additionally, the researchers plan to identify whether health events or patient characteristics are associated with occasional or high-use states.

Another presentation during the same session evaluated the impact of treatment adherence to HU on the quality of life (QOL) in younger patients with SCD. Adherence issues persist among younger patients⁵ receiving HU for SCD, and behavioral interventions are currently being tested in the field. The study⁶ was presented by Arlene Smaldone, PhD, CPNP-PC, CDE, Columbia University School of Nursing and College of Dental Medicine, New York, New York, and her colleagues.

The researchers examined barriers to HU adherence from the perspective of the sampled youth and their parents; these were poorly adherent youth aged 10 to 18 years and their parents who participated in the Hydroxyurea Adherence for Personal Best in Sickle Cell Disease (HABIT) trial, which had a 6-month intervention. In addition to self-reported barriers to HU at 0, 3, and 6 months following treatment initiation, the researchers evaluated the association between adherence and generic and disease-specific health-related QOL (HRQOL) markers. Further, the study examined whether a community health worker could reduce adherence barriers, and if so, how.

"Adolescence is a critical time to promote self-management," Smaldone said. "Little research has been done to identify barriers to HU use in both youth and their parents as a dyad," which they purported to evaluate with the current study.

"We used modified versions of 2 scales: the Adolescent Medication Barriers Scale [17 items; 3 subscales] and the Parent Medication Barriers Scale [16 items; 4 subscales]," Smaldone said. Barriers reported by $\geq 25\%$ of the sample were considered common, and parent proxy and youth-reported generic and disease-specific HRQOL were measured at the same intervals by the Pediatric Quality of Life Inventory (PedsQL) and PedsQL Sickle Cell Disease Module, respectively.

The study included 28 parent-youth pairs. The median age of the youth was 14.3 ± 2.6 years, 43% were female, and 50% had Latino origins. Overall, total barriers were greater for youth (5.0 ± 3.9) compared with parents (3.5 ± 3.2), and a majority of parents (82.1%) and the youth being treated (85.7%) reported at least 1 barrier to treatment with HU. »



PAULUKONIS

Susan Paulukonis, MA, MPH, program director, California Rare Disease Surveillance Program

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Further, a higher number of total barriers presented a significant inverse association with total generic HRQOLs in both parents ($r = -0.43$; $P = .03$) and the children ($r = -0.44$; $P < .001$). A similar inverse correlation was observed for disease-specific HRQOL among parents ($r = -0.53$; $P = .005$) and youth ($r = -0.53$; $P < .001$).

Smaldone highlighted some common barriers to HU use that were reported by the parents who participated in the study:

- Youth reliance on parent reminders (42.9%)
- Adolescent frustration from living with SCD (35.7%)
- Regimen adaptation (28.6%)
- HU beliefs, such as parental concern with impact of HU on either fertility or the fetus (25%)

Common youth-reported barriers included:

- Adolescent frustration from living with SCD (57.1%)
- Forgetfulness about taking HU (53.6%)
- Tired of taking HU (39.3%)
- Not wanting to take HU at school (28.6%)
- Not wanting to be seen taking HU at school (25%)
- HU ingestion issues:
 - Difficulty swallowing (25%)
 - Taking too many pills (39.3%)
 - Dislikes taste (35.7%)

- Regimen adaptation (28.6%)
- Knowledge deficits, such as not understanding how HU works (25%)

“The idea of being tired with living with the condition certainly resonated with both parents and the youth,” Smaldone said.

Although it was not a statistically significant difference, parents who were a part of the group that received the health worker intervention revealed a trend in less-reported adolescent frustration. Adolescents in the intervention group had lower ingestion-related barriers over the 6-month period (-0.17 per month; $P = .02$). However, total barriers and other subscale scores did not significantly change over the study period, Smaldone said.

Smaldone concluded that parents and youth had varying perspectives on HU barriers, based on what was reported as a part of their study, and that improved adherence to HU treatment would require that barriers of both parents and the youth be addressed. She noted, however, that their study was limited by a small sample size and the lack of assessment of factors, such as depression and depressive systems on QOL.

When their analysis controlled for group assignment and time, support lent by the community health workers helped youth to address HU ingestion barriers. The authors are currently conducting a multisite trial to test the complex

relationships between perceived barriers, HU adherence, and HRQOL. ♦

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COST OF CARE / BIOSIMILARS

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Biosimilar Beats Subcutaneous Rituximab on Cost Savings in NHL

Kelly Davio

THE LAUNCH OF BIOSIMILAR rituximab is an eagerly awaited event among US healthcare stakeholders who are cognizant of the high cost of intravenous (IV) administered rituximab in treating non-Hodgkin lymphoma (NHL).¹ At the same time, another innovation in rituximab delivery—a subcutaneously administered rituximab formulation—has the potential to save both cost and time.

During the 60th American Society of Hematology Annual Meeting & Exposition in San Diego, California, researchers presented findings from a time-and-cost simulation of subcutaneous rituximab (Rituxan Hycela), brand-name IV rituximab (Rituxan), and biosimilar IV rituximab from the US payer perspective.² The simulation analysis was performed for 1 patient with NHL over the course of 6 cycles of treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) using either standard or rapid infusion times.

The investigators derived costs of the subcutaneous and the IV reference rituximab products

from first-quarter 2018 average sales prices and 2018 reimbursement rates as listed in the Current Procedural Terminology code set. Costs for the proposed biosimilar were estimated at 15% to 35% discounts to the reference IV rituximab.

The investigators found that, following the first cycle of IV reference rituximab, switching to the subcutaneous formulation saves 650, 720, and 791 minutes (for patients with small, average, and large body sizes, respectively) over the next 5 cycles compared with continuing to use an IV option.

Costs for 6 cycles of R-CHOP, assuming a switch from the IV reference rituximab to the subcutaneous presentation at cycle 2, were \$54 higher than rapid infusion but \$104 lower than the standard infusion of the IV reference for patients with small body size. For patients with medium body size, the cost of subcutaneous administration was \$3854 and \$4012 lower than the cost of rapid and standard IV administration, respectively. For patients with large body size, the subcutaneous product saved \$7762 and \$7920 versus the 2 IV infusion speeds.

The investigators found that following the first cycle of IV reference rituximab, switching to the subcutaneous formulation saves 650, 720, and 791 minutes for patients with small, average, and large body sizes over the next 5 cycles, compared with continuing the IV option.

However, compared with an IV biosimilar rituximab, the subcutaneous option was costlier. For patients with small body size, the subcutaneous formulation cost between \$3647 and \$8649 more versus standard infusion and between \$3805 and \$8807 more versus rapid infusion of the biosimilar. For patients with medium body size, these ranges were \$325 to \$6109 and \$484 to \$6267 for the 2 infusion speeds. For patients with large body size, at a biosimilar discount of 25% or greater, subcutaneous

administration cost at least \$286 more than a standard infusion rate, and at a discount of at least 24%, at least \$116 more than the biosimilar delivered by rapid infusion.

The researchers concluded that, although subcutaneous rituximab in R-CHOP saves on both time and cost versus using the reference IV rituximab, using a biosimilar IV rituximab saves on costs versus subcutaneous administration in small- and average-sized patients at all levels of biosimilar discount, and in large patients if discounted by 25% and 24%.

In an email to The Center for Biosimilars®, the research team said that, although further

investigation is warranted to better evaluate whether these time and cost savings can be achieved in clinical practice, “we believe in the value of simulation models to advance our understanding of the potential time- and cost-savings for different formulations of oncology biosimilars. Further real-world evidence is essential in helping assess how biosimilars may help enable access to medicines for patients who may not otherwise afford them.

“What we can say,” added the authors, “is that biosimilar medicines are the future of health-care, providing vital treatments for prevalent, chronic cancer conditions. And, biosimilars deliver the same efficacy and safety that patients

and physicians trust and rely upon from reference biologics.” ♦

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Cost-Effective Use of White Blood Cell Growth Factors in the Veterans Administration

Kelly Davio

ALTHOUGH THE PROPHYLAXIS OF NEUTROPENIA is crucial for patients undergoing cytotoxic chemotherapy to maintain dose intensity of their anticancer regimens, using granulocyte colony-stimulating factor (G-CSF) agents does increase the cost of treatment. Long-acting G-CSF agents (such as pegfilgrastim) instead of short-acting agents (like filgrastim) has the potential to push costs even higher. For health systems like the Veterans Health Administration (VHA), where controlling costs while providing high-quality care is of heightened concern, achieving the best value for money in the prophylaxis of neutropenia can help to control the cost of cancer care.

During the 60th American Society of Hematology Annual Meeting and Exposition in San Diego, California, Kevin Knopf, MD, chairman of hematology/oncology at Highland Hospital in Oakland, California, and colleagues presented research on the most cost-effective approach to using G-CSF therapies in the VHA.¹

Knopf and his team surveyed 23 VHA sites on their use of brand-name filgrastim (Neupogen); tbo-filgrastim (Granix), a follow-on filgrastim that was approved prior to the establishment of the US' biosimilar approval pathway; biosimilar filgrastim (Zarxio); and brand-name pegfilgrastim (Neulasta). The researchers also estimated costs for the use of G-CSFs based on 340B pricing. Biosimilar pegfilgrastim was not included in this analysis.

The most cost-effective strategy, they found, was to use only tbo-filgrastim, as such an approach would result in a cost of \$62,336 per 100 patient episodes. Eighteen of the 23 surveyed sites used tbo-filgrastim as their preferred treatment, making the VHA 73% efficient and highly cost-effective. Costs for G-CSF use in each of the sites ranged from a minimum of \$62,336 per 100 patient episodes in 4 sites to a maximum of \$201,356 per 100 patient episodes at 2 sites, delivering a mean cost of \$99,080. Most sites, the researchers reported, were able to avoid the use of the long-acting and higher-cost pegfilgrastim; only 27% of patients across the surveyed hospitals had received Neulasta.

Furthermore, the adoption of biosimilar and follow-on filgrastim in the VHA has been rapid, the researchers said. None of the sites surveyed were using the brand-name filgrastim for new patients, and 6 of the 23 sites indicated that they were comfortable with switching patients who had previously received the branded filgrastim to a cost-saving option. Despite the willingness of the

VHA to adopt follow-on and biosimilar filgrastim, however, simply switching patients to tbo-filgrastim from the brand-name option provided only a small cost savings—just 2.2%—under 340B pricing.

According to the authors, other approaches to reducing the cost of G-CSF therapy are likely to have a greater impact on the overall cost of care than a switch to biosimilars. Such approaches include avoiding the use of G-CSF therapies in cases in which there is no convincing evidence of their efficacy (for example, in patients who are classified as low-risk), and continuing to use short-acting agents instead of long-acting ones whenever possible.

Furthermore, Knopf said in an interview with The Center for Biosimilars®, there is some limited evidence that it may be feasible to prevent neutropenia by using 2-day or 4-day courses of filgrastim rather than 8-day courses. He cited a nonrandomized trial conducted in the 1990s that found that, in patients with early breast cancer, the frequency of G-CSF administration could be shortened to just 2 administrations, on days 8 and 12, without altering the patients' outcomes.²

Knopf emphasized that further investigation will be necessary to demonstrate whether shorter treatment courses are indeed effective, such an approach could deliver an additional 50% to 75% cost savings. ♦

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KNOPF

Kevin Knopf, MD, chairman of hematology/oncology at Highland Hospital, Oakland, California.

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Biosimilar Filgrastim Performs in Stem Cell Mobilization

Samantha DiGrande

IN 2016, THE SASKATCHEWAN CANCER AGENCY switched from the brand-name filgrastim, Neupogen, to a biosimilar, Apotex's Grastofil, for stem cell mobilization prior to autologous stem cell transplants (ASCTs).

In a study presented at the 60th American Society of Hematology Annual Meeting, held December 1-4, 2018, in San Diego, California, researchers sought to determine the safety and efficacy of using a biosimilar for this setting.¹

In order to analyze the efficacy of the 2 products, the study's authors reviewed patient charts and compared the efficacy of CD34+ collection in 170 patients who received the brand-name filgrastim with 47 patients who received the biosimilar between 2012 and 2018.

They found that the brand name and the biosimilar demonstrated similar efficacy for stem cell mobilization, as 92.4% of the patients treated with the brand name product had a successful harvest (defined as a collection of 2x10⁶ or more CD34+ cells for patients planned for 1 stem cell transplant and 4x10⁶ or more CD34+ cells for patients planned for 2 transplants), compared with 100% of the patients taking the biosimilar.

In addition, the study's authors also looked at the efficacy of mobilization with both filgrastim products, either alone or in combination with

chemotherapy, in patients requiring more than 1 apheresis day and requiring the stem cell-stimulating agent, plerixafor. Clinical efficacy was defined in this portion of the study by using time to engraftment and length of hospital stay post-ASCT as parameters.

Importantly, the 2 products did not demonstrate a statistically significant difference in plerixafor requirement when patients had a low CD34+ count. There was also no statistically significant difference between each patient group that required more than 1 day of apheresis. In total, 59.4% of patients mobilized with the branded product required more than 1 apheresis day compared with 76.9% of patients mobilized with the biosimilar ($P = .11$).

Similarly, the researchers found that 42.5% of patients in the reference product group received chemotherapy, compared with 38.1% in the biosimilar group, a difference that was not statistically significant ($P = .71$).

In analyzing differences in length of hospital stay for patients, the researchers found that, again, there was no statistically significant difference. In patients taking the reference without chemotherapy, the median length of stay was 18.5 days (interquartile range [IQR], 17.0-21.0) compared with 19.0 days (IQR, 17.0-22.0) for patients taking the biosimilar without chemotherapy ($P = .10$). For patients also taking

"Due to the similar efficacy, prescribing a biosimilar over a reference product would be able to provide 'substantial cost savings to the healthcare system.'"

—Study authors

chemotherapy, lengths of hospital stays increased, but not in a statistically significant manner.

Based on these findings, the researchers determined that, when using either the biosimilar or the reference product for ASCT, each medication has similar efficacy. The study authors concluded that, due to the similar efficacy, prescribing a biosimilar over a reference product would be able to "provide substantial cost savings to the healthcare system." ♦

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COST OF CARE

Rapid Infusion of Daratumumab Offers Better Value in Multiple Myeloma, Researchers Find

AJMC Staff

A 2017 PRESENTATION by Barr et al demonstrated that after the first 2 infusions of daratumumab (Darzalex), the third infusion and beyond for patients with multiple myeloma could be shortened from 3.5 hours to 90 minutes.¹ At the 60th meeting of the American Society of Hematology in San Diego, California, researchers from the Taussig Cancer Center at Cleveland Clinic discussed what this change meant in terms of savings for health systems and improved quality of life for patients.²

The research team performed a retrospective chart review involving 181 patients with multiple myeloma who received daratumumab between February and June 2018 at the clinic. The change to rapid infusion of daratumumab began on April 24, 2018, and the team delineated infusions that took

place before and after that date. Forty-eight percent of the patients ($n = 86$) had longer infusions, and 52% ($n = 95$) had shorter infusions; these numbers cover 246 infusions at standard dosing and 305 as rapid infusions.

"Based on our financial data, we predict that will translate to approximately \$7000 in savings for the first 6 cycles of treatment if patients are started on rapid infusion ... with their third treatment dose," the authors wrote. An average of 2 hours of infusion time is saved for each visit, for an average of 610 hours saved over 2 months since the change in protocol and more than 3500 hours saved over 12 months.

Also, the authors said, "There have been dramatic improvements in quality of life and survival of

[patients with myeloma] with the introduction of novel therapies. This requires clinicians to adjust their framework of care to account for cost, quality, and value as it applies to patients, providers, and payers. Our analysis shows that with 2 hours less infusion time, both the direct and indirect costs savings are achieved." ♦

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QUALITY OF LIFE

Integrating Contemporary Palliative Care in the Treatment of Blood Cancers

Surabhi Dangi-Garimella, PhD

“PLACING PATIENTS IN THE CONTEXT of his or her family” and “caring for the living” were how palliative care was defined by one of the speakers participating in the Special Symposium on Quality at the 60th American Society of Hematology Annual Meeting & Exposition, held December 1-4, 2018, in San Diego, California. The speakers were tasked with reviewing the difference in the quality of symptom management, palliative care, and end-of-life (EOL) care delivered to patients with blood cancer and patients with other life-threatening illnesses.

Integrated palliative care, which combines care coordination for comorbidities, behavioral health issues, and EOL care, was proved to lend both symptom control and psychosocial support.¹ However, these services are not always readily accessible to patients, especially in rural areas and among populations with sparse access to medical care. Organizations like Project ECHO (Extension for Community Health Outcomes) are working to fill this gap.²

Additionally, controversy persists on whether patients with liquid cancers receive appropriate symptom management or whether they receive higher-intensity care, such as chemotherapy in the few weeks prior to death or a low hospice referral. Questions have also been raised over measuring the quality of symptom management and palliative care.

Palliative care is traditionally defined as “interdisciplinary care focused on improving the quality of life for persons of any age who are living with any serious illness, and for their families,” said Anthony O’Brien, MB, FRCPI, medical director of Marymount Hospice and consultant physician in palliative medicine at Cork University Hospital, Ireland, who was the first presenter.

Quality-of-life (QOL) is multifaceted and dynamic and changes over time. The traditional definition embraces patients of all ages and places the patient in the context of his or her family, O’Brien said.

O’Brien shared the clinical practice guidelines for quality palliative care, which he said are focused on life rather than death. The guidelines are:

- Have a family-centered approach to care
- Focus on physical, functional, psychological, practical, and spiritual consequences of a serious illness
- Build on the belief that early integration of palliative care improves QOL for patients and their families

“This is not a sequential approach, rather an integrated/concurrent model of care, alongside potentially curative treatment” that the patient is receiving, he added, defining palliative care as caring for the living rather than caring for a bodily organ, age, or lack of response to treatment.

“Beyond evidence-based medicine, palliative care is a model of interpersonal medicine that is effective and has narrative competence, where we try to understand the patient’s narrative,” O’Brien said. Pointing out that several organizations, including the American Society of Clinical Oncology, are committed to integrating palliative care in the main frame of healthcare systems, he added that such integration is extremely beneficial to patients within the context of their QOL, mood, satisfaction with care, symptom burden, and “sometimes survival.”

O’Brien concluded his talk by highlighting the discomfort of treating physicians in broaching this discussion, as was documented by a study that interviewed hematologists on the topic.³ The authors found that despite the positive attitude toward palliative care,

barriers included difficulty with defining the role of specialist palliative care services, which resulted in referral timing being determined by their personal confidence in providing EOL care. Additionally, the participating physicians indicated the lack of an inpatient palliative care unit as a barrier to offering palliative care to their patients. O’Brien firmly believes that families must plan for dying the same way they plan for the birth of a child, and he is a strong proponent of a frank dialogue between physicians and patients.

When it comes to measuring the quality of palliative services, however, Kelly Marie Trevino, PhD, assistant attending psychologist at Memorial Sloan Kettering Cancer Center, wondered whether existing measures are meaningful and sufficient to fulfill patient needs. Trevino believes that quality measures can be used to evaluate the processes being implemented throughout the administration of care, not just toward EOL.

Although the National Quality Forum’s focus for quality of palliative care includes safety, benefit, equity, timeliness, patient-centeredness, and efficiency of care, Trevino listed the measures that care providers currently use:

- Pain management: pain screening, pain assessment, patients treated with an opioid given a bowel regimen, and patients with advanced cancer assessed for pain during outpatient visit, with documentation of a discussion of spiritual/religious concerns that patients/caregivers did not want to mention
- Dyspnea management: dyspnea screening and treatment
- Care preference measures: patients in the intensive care unit who have documented care and treatment preferences
- Quality of care with EOL measures: comfortable dying, hospitalized patients who die an expected death with an implantable cardioverter defibrillator that has been deactivated, family evaluation of hospice care, and bereaved family survey

Providing an update on where the field currently stands, Trevino said that some of the existing quality measures are acceptable, but gaps persist. She particularly pointed out gaps in EOL care measures and the importance of patient-reported outcomes in this process, which she said are often underutilized in healthcare.

“There is inadequate attention to the disease trajectory as well. So, integration of palliative care from the beginning of treatment to EOL is important.” ♦

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O'BRIEN

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TREVINO

Kelly Marie Trevino, PhD, assistant attending psychologist, Memorial Sloan Kettering Cancer Center

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QUALITY OF LIFE

Treating R/R CLL With Ibrutinib Alongside CAR T-Cell Therapy Reduces Toxicity, Findings Show

AJMC Staff

PATIENTS WITH RELAPSED OR refractory (R/R) chronic lymphocytic leukemia (CLL) may have a new treatment option with chimeric antigen receptor (CAR) T-cell therapy, and for patients who have already been treated with ibrutinib, continuing the targeted therapy may decrease cytokine release syndrome (CRS), based on results presented at the 60th American Society of Hematology Annual Meeting & Exposition, December 1-4, 2018, in San Diego, California.

Researchers led by Jordan Gauthier, MD, treated a total of 43 patients, starting with 24 patients with CLL were treated with ibrutinib until their condition worsened and the targeted therapy was stopped. These patients were then treated with JCAR014, a CAR T-cell therapy being developed by Juno Therapeutics.

Then, the research team treated a second cohort of 19 patients with ibrutinib; this group was similar in age and level of disease as the first group. The second cohort started ibrutinib and stayed on it during CAR T-cell therapy and for 3 months afterward.

Gauthier and his colleagues reported the following results:

- 83% of the patients who took ibrutinib alongside CAR T-cell therapy had either a complete or partial response.
- 59% of the patients who took ibrutinib prior to CAR T-cell treatment, but stopped beforehand, had a complete or partial response to therapy.
- Administration of ibrutinib and JCAR014 was well-tolerated in most patients; ibrutinib was reduced or discontinued in 6 patients (35%) at a median of 21 days after the start of CAR T-cell infusion.
- One patient in the cohort taking ibrutinib with CAR T-cell therapy died due to fatal cardiac arrhythmia. One patient in the cohort that stopped ibrutinib before CAR T-cell therapy died from severe CRS and neurotoxicity.
- Although the percentage of patients with grade 1 CRS was the same between the 2 groups, the number was 26% higher in the

group that stopped ibrutinib before CAR T-cell therapy.¹

The authors said results must be confirmed in a larger study, but they expressed optimism with the findings. “To our knowledge, these are the most encouraging results that have been seen to date in humans with a combination of CAR T cells and a targeted agent,” Gauthier said in a press briefing.² “While the CAR T cells expanded robustly in both groups and led to high rates of response, we did not observe a single case of severe CRS in patients receiving ibrutinib during CAR T therapy.” ♦

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Teens, Young Adults With Public Insurance Linked to Worse Outcomes in Leukemia, Lymphoma

AJMC Staff

ADOLESCENTS AND YOUNG ADULTS (AYAs), defined as those 15 to 39 years of age, have not seen the same improvement in cancer survival as other age groups in recent decades. In addition, being uninsured or on public insurance, such as Medicaid, has been associated with worse overall survival than having commercial insurance.

Authors from the University of California, Davis, presented a study at the 60th American Society of Hematology Meeting & Exposition, held in San Diego, California, linking Medicaid to the California Cancer Registry to take a fresh look at these inter-related issues. The research team identified AYAs diagnosed with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, (HL) acute lymphocytic lymphoma (ALL), and acute myeloid lymphoma (AML) between 2005 and 2014. These patients were classified by what type of insurance they had, including whether they had Medicaid at diagnosis or whether they were not in Medicaid and had to enroll after their received their diagnosis.

Of the 11,667 patients in the study, 4435 had NHL, 4161 had HL, 1549 had ALL, and 1522 had

AML. Private insurance was most common among those with HL (66%) and NHL (60%), followed by AML (50%) and ALL (37%). Of the participants, 4059 had Medicaid, including 41% of this group who had been enrolled continuously, 43% who were enrolled upon diagnosis, and 15% who were not enrolled continuously throughout treatment. According to the authors, only 2% to 4% of patients, depending on diagnosis, remained uninsured.

Even after adjusting for socioeconomic factors, baseline comorbidities, and the type of facility where the patient was treated, patients with NHL or HL who received Medicaid discontinuously or upon diagnosis were more likely to have gotten their diagnosis at a later stage (either stage III or IV) than patients with other types of insurance. For patients with NHL, even having continuous Medicaid coverage—meaning those who were insured prior to diagnosis—had higher odds of late-stage disease. Similarly, having Medicaid at any point was associated with lower survival than private insurance. For AML, there was no similar link; for ALL, the association was seen with continuous Medicaid and other

types of public coverage, although discontinuous Medicaid trended toward significance.

“Our study demonstrates that a significant proportion of patients previously thought to have public insurance were discontinuously insured with Medicaid or uninsured at time of diagnosis, only receiving Medicaid after diagnosis,” the authors wrote. “While important, insurance enrollment at diagnosis does not provide the same prediagnosis access to services as those with continuous enrollment.”

“Medicaid, regardless of type of enrollment, was associated with worse survival in AYAs with NHL, HL, and ALL relative to private insurance. Therefore, future studies should focus on factors influencing worse outcomes for AYA patients with public insurance,” they wrote. ♦

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POLICY

ASH-EHA Joint Symposium Dives Deep Into the Leukemia–Down Syndrome Connection

Surabhi Dangi-Garimella, PhD

ALTHOUGH SEVERAL ASSOCIATIONS between constitutional syndromes, such as Down syndrome (DS), and predisposition to cancers have been recognized, recommendations for surveillance or clear association between the two are lacking. Speakers at a joint symposium between the American Society of Hematology (ASH) and the European Hematology Association (EHA), held December 2, 2018, during the 60th ASH Annual Meeting & Exposition in San Diego, California, highlighted the current understanding of cancer surveillance screening, as well as translational studies that target pathways in these and related hematologic malignancies.

“Children at high risk of developing myeloid leukemia within 4 years can be identified at birth based on the percentage of blasts and also by *GATA1* mutation analysis... A close liaison among hematologists, pediatricians, and neonatologists for guideline development would be important.”

—Irene Roberts, MD,
MRC Molecular Haematology Unit and Paediatrics,
MRC Weatherall Institute of Molecular Medicine

Between 5% and 30% of children with DS are born with transient leukemia of DS (TL-DS), also called transient myeloproliferative disorder.¹ Mutations in the transcription factor gene *GATA1*, in conjunction with trisomy 21 (T21), are key drivers of this myeloproliferative disorder. Research has shown that TL-DS may lead to early death in 15% to 23% of cases; survivors may develop acute myeloid leukemia (AML) of DS in the first 4 years of their life. Although guidelines for management of TL-DS were recently developed in the United Kingdom,² much remains to be discovered.

The first presentation during the joint session, “Leukemia in Down Syndrome: Why Does It Happen and Why Is It Important?” was by Irene Roberts, MD, MRC Molecular Haematology Unit and Paediatrics, MRC Weatherall Institute of Molecular Medicine, Oxford, United Kingdom.

There is increased susceptibility to leukemia in DS—both myeloid and lymphoid leukemias are common—and young children are especially susceptible, Roberts said. “The incidence ratio for AML is 12 in adults and 114 in children. On the other hand, the incidence of acute lymphoblastic leukemia is 13 in adults and 27 in children less than 4 years of age,” Roberts told the audience. The incidence is negligible in solid tumors.

For her talk, Roberts focused on AML. Myeloid leukemia of DS (ML-DS) originates in fetal life and presents before the child is 4 years. “It is preceded by a stage called transient abnormal myelopoiesis, or TAM,” Roberts explained. Development of TAM and ML-DS both require trisomy 21 and acquired *GATA1* mutations.

Neonatal preleukemia, she said, results from the N-terminal truncation of *GATA1* protein, called *GATA1s*, in T21 cells. Additional mutations cause ML-DS in persisting mutant *GATA1* cells and result in ML-DS before age 4.

What is the importance and relevance of leukemia in DS? Roberts listed several characteristics of this phenomenon, based on what is known in the literature combined with her laboratory’s findings:

- It provides a model of the natural history of leukemia within a defined time window
- It provides insight into *GATA1* function
- T21 leads to adapting to aneuploidy, gene dosage, and T21 in non-DS leukemias
- Constitutional syndromes with malignant potential are managed to implement research findings in the clinic
- There are policy and societal issues associated with this phenomenon beyond the leukemia itself.

Neonates with higher blasts and clinical TAM had more severe disease, as determined by using hepatomegaly, effusions, and splenomegaly. Disease severity was determined based on infiltration of tissue into mutant blast cells and fibrosis.

Roberts said that *GATA1* mutations in DS neonates predict for translation of *GATA1s*, which is the N-terminal truncated protein. It can lead to abnormal platelet production in DS neonates. Other characteristics of TAM are giant platelets and megakaryocyte fragments.

A significant finding is that *GATA1* mutations likely develop late in the second trimester or early in the third trimester of fetal development. The progression of TAM to ML-DS has several driver mutations, but the 2 most frequent mutations are in *Cohesin* and *CTCF*.

Roberts summed her findings by delineating clinical implications of the leukemia–DS relationship. “Children at high risk of developing myeloid leukemia within 4 years can be identified at birth based on the percentage of blasts and also by *GATA1* mutation analysis,” she said. This would also provide insight into those children who are at a low or no risk of developing myeloid leukemia, based on their blast count.

“A close liaison among hematologists, pediatricians, and neonatologists for guideline development would be important,” which she highlighted has recently been done in the United Kingdom.²

Presenting the developments in the United States was John D. Crispino, PhD, MBA, Division of Hematology and Oncology, Northwestern University, Chicago, Illinois.

GATA1, a zinc finger-binding transcription factor, is important for megakaryopoiesis, Crispino said, with N-terminal mutants leading to congenital dyserythropoietic anemia, congenital thrombocytopenia, and congenital erythropoietic porphyria. The *GATA1s* mutation can result in transient abnormal myelopoiesis, ML-DS, congenital hypoplastic anemia, and Diamond Blackfan anemia. The importance of *GATA1* in erythropoiesis is underscored by the fact that *GATA1*-deficient mice die of anemia, Crispino said.

Crispino’s laboratory conducted high-throughput studies in vitro to identify small molecule drugs that could target the *GATA1* deficiency in cells and to query if these drugs had disease-altering activity. Subsequent studies evaluated small molecule drugs that could force polyploidization in megakaryocytes and their »



CRISPINO

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ROBERTS

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maturation. This eventually led to the identification of Aurora kinase, which regulates cell cycle and proliferation, as a potential target, the inhibition of which can induce polyploidy and differentiation in megakaryocytic leukemia cells. Additionally, “the Aurora kinase inhibitor, alisertib, also caused a delayed differentiation-associated apoptosis,” Crispino said.

In mouse studies, primary human megakaryocyte leukemia cells are placed in mice, which were then treated with 2 cycles of alisertib and bone marrow was assayed at 27 days. The drug reduced immature human megakaryocytes in the mice and upregulated

the mature megakaryocytes. The study also found alisertib to have a survival effect.

Crispino’s group then treated a myeloproliferative neoplasms–AML cell line with alisertib and found that it increased both polyploidization and GATA1 protein expression. When mice injected with these cells were subsequently injected with 3 cycles of alisertib, the infiltrated mice had a high platelet count and transient increase in hemoglobin and hematocrit.

Because these studies identified Aurora kinase A as a therapeutic target in myelofibrosis, further studies are now evaluating the drug in the clinic.

“Can this strategy be used in the treatment of other GATA1 deficiency syndromes?” Crispino asked. This question remains unanswered. ♦

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NCI Director Highlights a Year of Progress in Hematology, Outlines Areas of Focus Going Forward

Jaime Rosenberg

“**NOW MORE THAN A YEAR** into the job, I’ve heard from a lot of stakeholders. I’ve heard from doctors and scientists, patients and advocates, and one clear fact from all those conversations is this: it is a great time to be a cancer scientist and a cancer doctor in the United States,” said Norman Sharpless, MD, director of the National Cancer Institute (NCI), as he addressed a crowd at the 60th American Society of Hematology Annual Meeting & Exposition held December 1-4, 2018, in San Diego, California.

Sharpless highlighted numerous recent advancements in the care of hematologic malignancies, including moxetumomab pasudotox-tdfk, a new treatment for hairy cell leukemia, which hasn’t had a new treatment option in 20 years, as well as the 2 chimeric antigen receptor T-cell therapies approved in the last year: tisagenlecleucel and axicabtagene ciloleucel.

He also brought attention to 2 NCI-supported trials of both younger and older patients with

chronic lymphocytic leukemia that identified a chemotherapy-free approach using rituximab and ibrutinib rather than drugs like bendamustine and fludarabine for these patients. “This is really important because we now have a relatively gentle regimen that works really well for these patients,” he said.

Sharpless called the past year an “extraordinary period” for acute myeloid leukemia, which came after decades of limited progress. In the last year and a half, the FDA has approved 8 new drugs for the disease, including 2 isocitrate dehydrogenase inhibitors, 2 Flt-3 inhibitors, and venetoclax.

Advancements like these are a result of detailed, elegant basic science, according to Sharpless. “There’s this great basic science that’s developing in hematologic cancers, and these scientific developments are translating into meaningful therapies for patients,” he said.

However, despite this progress, many will rightly say it’s not enough, said Sharpless, with many of

these new therapies being only moderately effective and sometimes not curative. He called these therapies singles and doubles, noting that we still need home runs.

Following a listening tour to hear from stakeholders across the hematologic landscape, Sharpless identified areas that, while they are not new concepts, we need to sharpen our focus on in the next few years. He outlined 4 focus areas:

1. *Workforce development*: Supporting the cancer research enterprise by focusing on the workforce cancer investigators
2. *Basic science*: Reaffirming the NCI’s commitment to basic science to drive novel approaches and technologies
3. *Big data*: Increasing data aggregation and interpretation to speed work across the cancer enterprise
4. *Clinical trials*: Fully realizing the power of clinical trials through innovative design, administration, and analyses ♦

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Produced by Samantha DiGrande and Jaime Rosenberg

NOTE: this section has been edited for clarity

Ted Okon, Executive Director, Community Oncology Alliance



What are some policy priorities for the Community Oncology Alliance (COA) in 2019?

I think the top priorities when you look at COA, and as we move into 2019, are going to be surrounding these middlemen. These pharmacy benefit managers have gotten so brazen, and we have more examples of where cancer patients cannot get their medications on time or at all, or get the wrong dose or too much of the medication.

I saw one case recently where a patient received \$172,000 of drugs that were totally wasted. So, we're going to be looking at this and we're going to be looking at these middlemen getting in the way of the patient and the physician making a decision about their therapy.

We're seeing too many preauthorizations being held up, so this is a top priority. We're very concerned about the federal government now giving these middlemen more power, especially in Part B, which is chemotherapy delivered in the physician's office.

We will be all over that, and any proposals at all that get in the way of the physician and the patient making informed decisions and going ahead with timely cancer treatment. ♦

Lalan Wilfong, MD, Executive Vice President of Quality Programs, Texas Oncology



What are some key learnings in the Oncology Care Model (OCM) and how can they be applied to other reform models?

There have been a lot of key learnings from the OCM and how it would relate to other payment models. One is that attribution is key and making that an easy process for the practices. They have to know that the patients they enroll in the model are in the model and have that collaboration with the payer to make sure that the attribution is done well and done quickly for the practice.

Looking at total cost of care is difficult, and figuring out what the practice is and is not responsible for can be very difficult to do. Case mix is a huge issue as well; with breast cancer, for example, there can be quite a lot of variation in the appropriate price of care for different patient populations. Especially for small practices with small populations, just a little bit of a case-mix difference can cause huge variations in the total cost of care.

I think the big key learning is that whatever payment model you're in requires significant collaboration between the practice and the payer. A lot of trust has to go into that relationship—trust that the payer will give you timely information, and trust that the practice will do what they say they will do and really look at improving the value that they provide to the patients.

What is the struggle for reimbursement for new innovative cancer therapies?

The cost of cancer care is rising dramatically, and the cost of new innovative cancer therapies is quite high for many reasons. It's difficult to address that in

a practice because we don't control the cost of care. You just want to provide the appropriate care for the appropriate patient at the appropriate time—that's the mantra for taking good care of patients.

It's a difficult question to figure out how we can address that in the care that we provide. I think pathways is one way to do that, where we can look at what an appropriate, new, innovative therapy is and which patient population it should be given to. Doing innovative payment adjustments is also important so the practices aren't discouraged from using novel therapies where appropriate. I think the challenge is figuring out which novel therapies are appropriate for which patients and making sure you're utilizing them appropriately for the patients that you have.

What has been Texas Oncology's experience with the OCM thus far?

The OCM has been challenging for Texas Oncology—as it has been for all practices—but it did make us stop and think about how to take care of patients and be more patient-centric than we ever have been before.

A lot of good has come out of the program for us: having shared decision making with patients, really thinking about the cost of care, and having access for our patients [to go to] our clinics to avoid hospitalizations and emergency departments; all of which has been very good for our patients and the patient care that we provide.

The things we've succeeded in are simply those—making sure that we have access to our patients, making sure that we keep them out of the hospital and the emergency department—and we have done really well in those areas and have shown improvement over time in those areas for patient care.

We've done some very simple things for drug utilization—drugs are a big cost of cancer care—and we've done some very simple things for managing drugs and utilization. For example, using pathways and looking at other drugs, like antiemetics and growth factors, and making sure we're using those appropriately.

What we're challenged with right now is that next step, that next hurdle where things get a little bit more complicated. I feel like we've done the easy things, and the things that are easy to rally around and do well with for the practice, but now we've got to start making some very tough decisions to make that next hurdle and really succeed in the program. ♦

Bo Gamble, Director, Strategic Practice Initiatives, Community Oncology Alliance



How does the Community Oncology Alliance (COA) view "value" in oncology, and how is that distinction determined?

That's a great question, and it's a question that we often get asked. COA's perspective on value is: let's ask all of the different stakeholders, and let's try to come up with a model that can meet that statement or meet the value guide for everyone (whether they're a patient or an employer. A patient has their own set of values, providers have their own set of values, and the people that pay for it have their own set of values.

So, let's come together and make sure we understand that, especially when we present the model and all the options for whatever your definition [of value] may be. To us, there's no simple definition. But the model, »

the payment system, and the delivery system need to consider all of the different aspects of value.

Where do you think the future of the Oncology Care Model (OCM) is headed? How will the design model change?

I think the OCM will live its life for the next 2.5 years. They have been fairly vocal about living out the life of the model. So, it'll end 2.5 years after this December, and then they'll have to read reports, and maybe 3 years or 2.5 years after that they'll come to a conclusion, "OK, well what did we learn?" Now, that's a lifetime to me as far as reform goes.

We're trying to learn from what we've seen so far, what they've done well, and what they struggled with, and then create sort of a baseline or a template for changing the way cancer care is to be reviewed and rewarded for everyone, not just Medicare. So, that means making it simpler—hopefully—and communicating and communicating and communicating again, because you're going to have to. Introducing different participants, maybe national payers, is something we haven't done in the past; maybe some big employers as well, to give them the tools to get started.

We've learned a lot from the complexity of this one and the communication (or sometimes the lack thereof). Sometimes they're a little too rigid when making changes—and at times they need to be—but sometimes they need to talk through some solutions and try to make it better for everyone. It needs to change; they're doing a great job trying to get that process started, but we need to finish that process. ♦

Lyn Fitzgerald, Senior Vice President, US & Global Development, National Comprehensive Cancer Network



Do you think there should be greater adoption of risk-based models, and if so, why?

In a study I had read, there was, I believe, a 23% increase over the past 2 years, so there is a growth rate relative to adoption of alternative payment models. But relative to risk, the question is preparedness. I'm not quite certain that the system is equipped to provide a comfort level for clinicians so that they're ready to take on 2-sided risk.

For example, something that was published in your journal, I think it was in April, David Nash from Jefferson talked about why providers were not willing to take on 2-sided risk. It was that they felt they did not have control over variation and quality within the system, and also that their lack of control was overestimated. I believe that has to do with a lack of infrastructure, so the technology is not there; the data and the feedback around medical information and claims information to allow a practice or a health system to prepare may not be there in the broader scheme for there to be wider adoption at more than the pace we're moving at now.

How is the National Comprehensive Cancer Network (NCCN) working to define and assess "value" in cancer care?

So, in 2015, NCCN introduced the NCCN Evidence Blocks, which is a tool that allowed for clinicians and patients to have a conversation about what is important to a patient's individual value system. We'd consider the efficacy of a therapy, safety, quality of the evidence, consistency of the evidence, and affordability.

The categories of preference are another step; it's another tool to help clinicians understand what optimal care is. We believe that value truly is defined by an individual patient's need, and so the categories of preference allow for our panel members to signal to clinicians, of all the recommendations in the NCCN guidelines, which are the preferred ones.

What is the struggle with reimbursement for new innovative cancer therapies?

You know, it's interesting, because my feeling is that doctors want to do what's right by patients, and doctors are evidence-driven. And so, truly the greatest

thing that can help a provider feel comfortable providing an innovative therapy to a patient is the evidence behind that therapy.

So whether they're in the [Oncology Care Model] or any type of alternative payment model, the strength of the evidence is the strength of the efficacy. The outcomes will drive the use of that innovation. ♦

Elizabeth Griffiths, MD, Associate Professor of Oncology, Department of Medicine, Roswell Park Comprehensive Cancer Center



How are mutational data helping inform clinical prognosis and treatment protocol?

I think we're beginning to understand that mutational profiles can tell us something about the character of the leukemia. Historically, we [defined] patients as either fit for induction or unfit, and we made therapy decision largely based on those clinical factors. Using mutational profiles, we can actually identify patients whose disease is likely to be intransigent to conventional chemotherapies, and with that approach, we can actually slate patients to receive therapies that are more likely to benefit them.

So, instead of giving them traditional cytotoxic therapies, which tend to have a very low rate of remission induction, in say, patients with p53-mutant disease or complex karyotype. We might offer them an alternative induction strategy, potentially with a novel therapeutic combination, like one of the venetoclax combinations. I think that recognition is likely to change the way we approach patients in the future.

Right now, a fit patient would still likely be offered a conventional induction strategy or Vyxeos, the CPX-351 liposomal cytarabine–daunorubicin combination. But perhaps in the future, we might be able to change our approach.

I think the molecular profiling has also unveiled a variety of targets that we can use in combination with traditional chemotherapeutics. So, as highlighted by Keith W. Pratz, MD, associate professor of oncology, Johns Hopkins University, and Eytan Stein, MD, hematologic oncologist, Memorial Sloan Kettering Cancer Center, up-front combinations of both novel FLT-3 inhibitors and IDH [isocitrate dehydrogenase] inhibitors with conventional chemotherapy like 7+3 can provide really substantial rates of remission induction success and potentially deep molecular emissions, which may translate into better long-term survival for patients. ♦

Kavita Patel, MD, MS, Nonresident Senior Fellow, Brookings Institution



How has the Oncology Care Model (OCM) evolved? What do you think it does well, and what are some of the pain points that participating practices continue to face?

The OCM has evolved in a couple of interesting ways. Data are now a very regular kind of term with the OCM practices. Almost all of them have done something with the access to claims data that they have, so that's actually progress.

The second thing that they've all noticed is that these transformation activities—care transformation and quality improvement—are all actually working. Not necessarily in the way they might have thought, but they're making patients feel like they're getting better care and, in some cases, they're delivering on improvements in quality measures.

The thing that's still not working as well is this kind of clunkiness with things like attribution. It takes a long time—there's a lag in how CMS processes the

data about attribution and what we call reconciliation. It might take doctors up to about 18 months to ultimately know if the patient they thought they were taking care of is actually acknowledged by Medicare as their patient, and then vice versa. People that they thought were their patients are not necessarily theirs, and they don't find out until about a year later. So, there are still some clunky things that have to do with how Medicare just processes claims under the model.

Can you discuss some of the key trends from the OCM's second performance period results?

Practices overall are doing better, but it's not like it's a massive shift. There were improvements from the first to second performance period, but we ultimately haven't seen a large majority of practices with improvements. Now, what I don't know about is the financial; CMS doesn't publish the financial improvements, so you're hearing kind of fits and spurts about practices saving money that did not save it before.

So overall, I would say if I were sitting in CMS's shoes, I'd be like, "Yes, this program is still working and it's working well." I don't know if it's necessarily "meeting the expectations" of what people thought they would be when they started the OCM, but I spend a lot of time looking at all of CMS' models and this is a model that's doing pretty well compared to [accountable care organizations and some others. So even I would step back from performance period 2 and say that this is a model that's working. ♦

Theresa H.M. Keegan, PhD, MS, Associate Professor, Hematology and Oncology, University of California, Davis, Comprehensive Cancer Center



How represented are adolescents and young adults in clinical trials?

Overall, AYAs, which are adolescents and young adults—and we typically define that as 15 to 39 years of age—are less represented in clinical trials than children. So, back in 2006, we reported that 14% of

AYAs participated in clinical trials. This was using population-based data in the Surveillance, Epidemiology, and End Results Program. This is in contrast to children, where approximately 90% are treated at institutions with NCI [National Cancer Institute]-sponsored clinical trials and as many as two-thirds [are] participating in clinical trials. So, there's pretty dramatic differences by age, in terms of clinical trial participation.

Has representation changed over recent years?

So, not really, actually. Part of our goal was to look at changes over time. There's been substantial efforts to increase both access to and participation for AYAs in clinical trials, and this is really because we've noticed less improvement in AYAs in survival over the past 30 years, and this has been attributed to lower participation in clinical trials as well as a number of other factors.

So, our goal was to look to see if we have seen an increase in participation over time. We were able to do some work ourselves in population-based data and found that in 2012 and 2013, we saw a modest increase from 15% to 18%, and these were in patients with acute lymphoblastic leukemia [ALL], Hodgkin, non-Hodgkin lymphoma patients, and sarcoma. But really, no significant increases over time.

There was a suggestion that there is an increased participation in ALL trials, and this has been noted by others. So, that may be the one exception; that for those patients that there is some increase in trial accrual. And there has been a lot of attention given to adolescent and young adult patients with ALL. But again, overall and in general, we don't see increased clinical trial participation. ♦

Jeff Sharman, MD, Medical Oncologist, Willamette Valley Cancer Institute and Research Center; Medical Director, The US Oncology Network



How does the standard of care for CLL differ based on treatment setting?

Chronic lymphocytic leukemia [CLL] is a slow-growing disease. It takes a long time for many patients to have their disease grow to a point where it needs treatment, and when patients need their first-line

therapy, there are a lot of choices out there, and they're broadly divided into a chemoimmunotherapy approach or a targeted-agent approach.

We're going to see information in the plenary session that that exact question is being addressed in a study where patients get either ibrutinib, ibrutinib and rituximab, or bendamustine and rituximab. The findings of the study, and this is kind of somewhat an older population, is that the progression-free survival would appear to favor those patients treated with ibrutinib compared with chemoimmunotherapy.

But if you dive a little bit deeper and look at the different types of subgroups—and as we begin to talk about personalized medicine, there are some markers where the benefit of ibrutinib over chemoimmunotherapy is very clear—there are other groups where you can make an argument for a fixed-duration chemoimmunotherapy-based approach.

When you get to the relapsed setting, it really does tend to favor more of the novel targeted therapies, such as ibrutinib or venetoclax, compared with chemotherapy-based treatment.

How has the era of personalized medicine changed the way you think about treatment for patients with CLL?

Personalized medicine is a complex topic because what it generally refers to is a notion that you might find some feature or marker that's unique to a patient and then select therapy on the basis of that marker. In the case of chronic lymphocytic leukemia, the disease is divided primarily into 2 groups of patients: those who have what's called a mutated B-cell receptor and those who have an unmutated B-cell receptor.

In this case, mutation is good. It means you tend to have a slower-growing disease, fewer high-risk genetic markers for chemotherapy resistance, and so forth. So, by looking at the *IGHV* [immunoglobulin heavy chain variable] mutation or the B-cell receptor mutation status, those patients who have mutated disease are generally those patients who are going to benefit from a chemoimmunotherapy approach, whereas the patients who are unmutated are going to clearly benefit more from the novel targeted agent approach.

I think that there is debate, frank debate within the field, even amongst those who know the disease best, as to whether or not those patients with the mutated disease should get ibrutinib [Imbruvica] or chemoimmunotherapy, and I think that in a lot of cases, that would be subject to patient preference. ♦

Robert M. Rifkin, MD, FACP, Medical Director, Biosimilars; Associate Chair, Hematology Research, McKesson Specialty Health



What are the most recent treatment advances in multiple myeloma?

This year's [American Society of Hematology Annual Meeting & Exposition had] many significant advances in multiple myeloma. Everybody will hear a lot about CAR [chimeric antigen receptor] T-cell therapy, but

unfortunately, we're not curing anybody with that and the responses are lasting sometimes long, sometimes short. Another big focus will be the bispecific antibodies, or the BiTE molecules. Several of these are in development, early clinical trials. »

Probably the hottest target of the whole meeting will be the BCMA target in multiple myeloma, which is the B-cell maturation antigen. So, there will also be many presentations on agents directed for BCMA, some monoclonal antibodies, some antibody-drug conjugates. So, it's exciting, in terms of the advances that we've made.

In terms of new drug approvals, it's not quite the banner year it was a year ago, but [there're] still many new agents entering the market and many exciting things to come.

How are these advances impacting clinical outcomes?

So, a lot of these are really new. In most of the trials, we barely know progression-free survival. There will be some early overall survival data being presented with new chemotherapy regimens, but we really have to wait and see the impact. I think it will also be extraordinarily important to control cost as all of these new agents come out.

There was one oral presentation on a quadruple combination of therapy, which works very, very nicely, but there was little, if any, mention of the financial impact on the patient and the healthcare system. So, in multiple myeloma, we're going to have to get more responsible as all of these new agents march quickly to the forefront. ♦

Alison J. Moskowitz, MD, Medical Oncologist, Clinical Director, Lymphoma Inpatient Unit, Memorial Sloan Kettering Cancer Center



How important is it to engage patients with Hodgkin lymphoma so that they understand their diagnosis and their treatment options?

I think it's incredibly important that patients understand their diagnosis and what the treatment options are and what their prognosis is. I think that the treatment options that we have to offer patients are often not straightforward and not black-and-white where there's one right or wrong answer. Some of it really has to depend upon the patient's own values and their own choices.

One example of that is when we are offering patients with early-stage Hodgkin lymphoma a treatment approach where we're going to consider either combined modality therapy, where we include radiation therapy, or chemotherapy alone. That is an important discussion to have with the patients, because the cure rate with chemotherapy alone for early-stage Hodgkin lymphoma is not as high as when we use combined modality therapy. But by eliminating the radiation, we are reducing long-term toxicity. But there's a small group of patients who are going to relapse and then going to need much more intense chemotherapy and a stem cell transplant in order to cure their disease at that point.

So, even though the majority of patients still will be cured with chemotherapy alone, it's an important discussion to have with the patients to make sure they understand what they're potentially giving up if they're not getting radiation earlier on in their treatment.

I think it's perfectly reasonable to avoid radiation for many, many patients, but I think we have to be informing patients why we're making this choice and have them be a part of that choice as well.

Are there any disparities in survival among patients with Hodgkin lymphoma?

There are disparities with regard to survival. Patients who are over 60 [who have] Hodgkin lymphoma have much lower survival than patients who are under 60, and that has been found partly because the biology of the disease may be a little different. But the major reason is because of reduced tolerability to treatment and more toxicity related to treatment and likely also due to more comorbidities.

So, our treatment for patients who are over 60 tends to be modified a little bit. One of the things we really try to be careful with [in] those patients is exposing them to bleomycin because they do have a higher chance of having bleomycin lung toxicity. So, one approach could be to try to still expose them

to bleomycin but try and reduce it as much as possible, which is possible if we use the approach where patients receive 2 cycles of regular ABVD [doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine] chemotherapy. And if they have a PET [positron emission tomography]-negative response, then we drop bleomycin for further treatment. For some patients, we really want to try to avoid bleomycin all together. It's not unreasonable to give them just AVD [doxorubicin, vinblastine, and dacarbazine] chemotherapy without the bleomycin. It's probably associated with a less favorable outcome but still could be curable. ♦

Irene Roberts, MD, Professor of Pediatric Hematology, MRC Molecular Hematology Unit and Pediatrics, MRC Weatherall Institute of Molecular Medicine.



How at risk are patients with Down syndrome for developing leukemia compared with the general population?

That very much depends on the age. So, for example, in a lifetime, say up to age 60, there's about a 12-fold increased risk of acute myeloid leukemia compared with individuals without Down syndrome and a 13-fold increase of acute lymphoblastic leukemia. But if you're a young child, the statistics are a lot different. So, the risk of a myeloid leukemia in children under 4, for example, climbs to 114-fold compared with other young children who don't have Down syndrome.

What's the reason behind this risk?

That's a very good question, and we don't fully know the answer, and a lot of people are researching on that. The assumption is that it has something to do with the extra chromosome in the blood cells. So, having an extra chromosome, 21, in some way affects the behavior of the blood cell, which makes it more likely to transform. But which genes do it, we still don't know. ♦

Jennifer R. Brown, MD, PhD, Director, Chronic Lymphocytic Leukemia Center, Dana-Farber Cancer Institute, and Associate Professor of Medicine at Harvard Medical School



Does genomic sequencing play a role in determining prognosis and treatment for patients with chronic lymphocytic leukemia (CLL)?

Certainly, certain genomic prognostic markers are quite important in CLL. Historically, we've used chromosome abnormalities as determined by FISH [fluorescence in situ hybridization], with the highest-risk abnormality being the deletion of 17p. Now, that's often accompanied by mutation of the *TP53* gene, which we now recognize [as] being similarly adverse to 17p deletion. One thing that was remarkable about venetoclax [Venclexta] and rituximab [Rituxan] is that there was no difference in progression-free survival [PFS] at 2 or 3 years based on 17p deletion.

That's actually even better than the BTK [Bruton tyrosine kinase] inhibitors, where we actually do see that PFS is a bit shorter in the patients with that very high-risk marker. There are other gene mutations in CLL, as well. *NOTCH1* is one that we worry about associated with Richter transformation, *SF3B1*, and *ATM*. And then [there is] a long list of less frequent mutations. We don't really know yet what the impact of those are in the context of novel agent therapy, and that's something that we're all very interested still in studying. ♦

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