SPECIAL ISSUE: **ASH MEETING RECAP**

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AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based ONCOLOGY™

JANUARY 2017
VOL. 23 • NO. 1

HIGHLIGHTS FROM THE MEETING

- CAR T-cell updates in CLL and preventing cytokine release syndrome in patients treated with CAR T
- Updates on the LyMa and RESONATE-2 trials
- NCI-MATCH and Beat AML: new trial designs to maximize patient access to cancer treatments using a precision approach
- Improving healthcare delivery by employing health information technology
- How can nurse practitioners and physician assistants improve quality of care and patients access?
- ASH *Choosing Wisely*® Champions

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ANNOUNCING

A Permanent J-code for EMPLICITI™ (elotuzumab) – J9176

for injection, for intravenous use (300 mg and 400 mg vials)

J-code for EMPLICITI

HCPCS Code	Description	Effective
J9176[1]	Injection, elotuzumab, 1 mg	January 1, 2017

J9176 replaces HCPCS code C9477, injection, elotuzumab 1 mg, and also miscellaneous codes J9999, J3590, and J3490.[1]

NDC Codes for EMPLICITI[2]

0003-2291-11, 00003-2291-11	Single-dose vial containing 300 mg of lyophilized powder
0003-4522-11, 00003-4522-11	Single-dose vial containing 400 mg of lyophilized powder

For more information:

- Contact your **Area Reimbursement Manager** for general assistance and to schedule an office visit
- Call Bristol-Myers Squibb Access Support® at **1-800-861-0048** 8 AM to 8 PM ET, Monday-Friday, to speak with your dedicated team of regionally assigned specialists
- Visit **www.BMSAccessSupport.com** for information and resources, including the BMS Access Support program enrollment form, to help your patients with access to Bristol-Myers Squibb oncology products

The accurate completion of reimbursement- or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol-Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item. This coding guidance is not intended to provide specific directions on requesting prior authorization or submitting claims for EMPLICITI and does not provide a guarantee of receiving prior authorization or reimbursement. Coding for EMPLICITI is dependent on the insurer and the care setting in which the drug will be administered. Oncology practices need to make coding decisions based on the diagnosis and treatment of each patient and the specific insurer requirements.

Indication

EMPLICITI is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

Select Important Safety Information

EMPLICITI with lenalidomide and dexamethasone is associated with the following Warnings and Precautions: Infusion Reactions, Infections, Second Primary Malignancies, Hepatotoxicity, Interference with Determination of Complete Response, Pregnancy/Females and Males of Reproductive Potential, and Adverse Reactions.

References

1. American Medical Association. *2016 HCPCS Level II, Professional Edition*. Chicago, IL: American Medical Association; 2016.
2. EMPLICITI [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Please see additional Important Safety Information and brief summary of Full Prescribing Information on the following pages.

IMPORTANT SAFETY INFORMATION

Infusion Reactions

- EMPLICITI™ (elotuzumab) can cause infusion reactions. Common symptoms include fever, chills, and hypertension. Bradycardia and hypotension also developed during infusions. In the trial, 5% of patients required interruption of the administration of EMPLICITI for a median of 25 minutes due to infusion reactions, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had them during the first dose. If a Grade 2 or higher infusion reaction occurs, interrupt the EMPLICITI infusion and institute appropriate medical and supportive measures. If the infusion reaction recurs, stop the EMPLICITI infusion and do not restart it on that day. Severe infusion reactions may require permanent discontinuation of EMPLICITI therapy and emergency treatment.
- Premedicate with dexamethasone, H1 Blocker, H2 Blocker, and acetaminophen prior to infusing with EMPLICITI.

Infections

- In a clinical trial of patients with multiple myeloma (N=635), infections were reported in 81.4% of patients in the EMPLICITI with lenalidomide/dexamethasone arm (ERd) and 74.4% in the lenalidomide/dexamethasone arm (Rd). Grade 3-4 infections were 28% (ERd) and 24.3% (Rd). Opportunistic infections were reported in 22% (ERd) and 12.9% (Rd). Fungal infections were 9.7% (ERd) and 5.4% (Rd). Herpes zoster was 13.5% (ERd) and 6.9% (Rd). Discontinuations due to infections were 3.5% (ERd) and 4.1% (Rd). Fatal infections were 2.5% (ERd) and 2.2% (Rd). Monitor patients for development of infections and treat promptly.

Second Primary Malignancies

- In a clinical trial of patients with multiple myeloma (N=635), invasive second primary malignancies (SPM) were 9.1% (ERd) and 5.7% (Rd). The rate of hematologic malignancies were the same between ERd and Rd treatment arms (1.6%). Solid tumors were reported in 3.5% (ERd) and 2.2% (Rd). Skin cancer was reported in 4.4% (ERd) and 2.8% (Rd). Monitor patients for the development of SPMs.

Hepatotoxicity

- Elevations in liver enzymes (AST/ALT greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were 2.5% (ERd) and 0.6% (Rd). Two patients experiencing hepatotoxicity discontinued treatment; however, 6 out of 8 patients had resolution and continued treatment. Monitor liver enzymes periodically. Stop EMPLICITI upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.

Interference with Determination of Complete Response

- EMPLICITI is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

Pregnancy/Females and Males of Reproductive Potential

- There are no studies with EMPLICITI with pregnant women to inform any drug associated risks.
- There is a risk of fetal harm, including severe life-threatening human birth defects associated with lenalidomide and it is contraindicated for use in pregnancy. Refer to the lenalidomide full prescribing information for requirements regarding contraception and the prohibitions against blood and/or sperm donation due to presence and transmission in blood and/or semen and for additional information.

Adverse Reactions

- Infusion reactions were reported in approximately 10% of patients treated with EMPLICITI with lenalidomide and dexamethasone. All reports of infusion reaction were Grade 3 or lower. Grade 3 infusion reactions occurred in 1% of patients.
- Serious adverse reactions were 65.4% (ERd) and 56.5% (Rd). The most frequent serious adverse reactions in the ERd arm compared to the Rd arm were: pneumonia (15.4%, 11%), pyrexia (6.9%, 4.7%), respiratory tract infection (3.1%, 1.3%), anemia (2.8%, 1.9%), pulmonary embolism (3.1%, 2.5%), and acute renal failure (2.5%, 1.9%).
- The most common adverse reactions in ERd and Rd, respectively (>20%) were fatigue (61.6%, 51.7%), diarrhea (46.9%, 36.0%), pyrexia (37.4%, 24.6%), constipation (35.5%, 27.1%), cough (34.3%, 18.9%), peripheral neuropathy (26.7%, 20.8%), nasopharyngitis (24.5%, 19.2%), upper respiratory tract infection (22.6%, 17.4%), decreased appetite (20.8%, 12.6%), and pneumonia (20.1%, 14.2%).

Please see brief summary of Full Prescribing Information on following pages.

EMPLICITI™ (elotuzumab) for injection, for intravenous use ℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

EMPLICITI (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

CONTRAINDICATIONS

There are no contraindications to EMPLICITI. Because EMPLICITI is indicated for use in combination with lenalidomide and dexamethasone, healthcare providers should consult the prescribing information of these products for a complete description of contraindications before starting therapy.

WARNINGS AND PRECAUTIONS

Infusion Reactions

EMPLICITI can cause infusion reactions. Infusion reactions were reported in approximately 10% of patients treated with EMPLICITI with lenalidomide and dexamethasone in the randomized trial in multiple myeloma. All reports of infusion reaction were Grade 3 or lower. Grade 3 infusion reactions occurred in 1% of patients. The most common symptoms of an infusion reaction included fever, chills, and hypertension. Bradycardia and hypotension also developed during infusions.

In the trial, 5% of patients required interruption of the administration of EMPLICITI for a median of 25 minutes due to infusion reactions, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had them during the first dose.

Administer premedication consisting of dexamethasone, antihistamines (H1 and H2 blockers) and acetaminophen prior to EMPLICITI infusion *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Interrupt EMPLICITI infusion for Grade 2 or higher infusion reactions and institute appropriate medical management *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Infections

In a clinical trial of patients with multiple myeloma (N=635), infections were reported in 81.4% of patients in the EMPLICITI combined with lenalidomide and dexamethasone (E-Ld) arm and 74.4% in lenalidomide and dexamethasone (Ld). Grade 3 to 4 infections were noted in 28% and 24.3% of E-Ld- and Ld-treated patients, respectively. Discontinuations due to infections occurred in 3.5% of E-Ld-treated and 4.1% of Ld-treated patients. Fatal infections were reported in 2.5% and 2.2% of E-Ld- and Ld-treated patients.

Opportunistic infections were reported in 22% of patients in the E-Ld arm and 12.9% of patients in the Ld arm. Fungal infections occurred in 9.7% of patients in the E-Ld arm and 5.4% of patients in the Ld arm. Herpes zoster was reported in 13.5% of patients treated with E-Ld and 6.9% of patients treated with Ld. Monitor patients for development of infections and treat promptly.

Second Primary Malignancies

In a clinical trial of patients with multiple myeloma (N=635), invasive second primary malignancies (SPM) have been observed in 9.1% of patients treated with E-Ld and 5.7% of patients treated with Ld. The rate of hematologic malignancies were the same between E-Ld and Ld treatment arms (1.6%). Solid tumors were reported in 3.5% and 2.2% of E-Ld- and Ld-treated patients, respectively. Skin cancer was reported in 4.4% and 2.8% of patients treated with E-Ld and Ld, respectively. Monitor patients for the development of second primary malignancies.

Hepatotoxicity

Elevations in liver enzymes (aspartate transaminase/alanine transaminase [AST/ALT] greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were reported in 2.5% and 0.6% of E-Ld- and Ld-treated patients in a clinical trial of patients with multiple myeloma (N=635). Two patients experiencing hepatotoxicity were not able to continue treatment; however, 6 out of 8 patients had resolution and were able to continue treatment. Monitor liver enzymes periodically. Stop EMPLICITI upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.

Interference with Determination of Complete Response

EMPLICITI is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions]*. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the label:

- Infusion reaction *[see Warnings and Precautions]*.
- Infections *[see Warnings and Precautions]*.
- Second Primary Malignancies *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.
- Interference with Determination of Complete Response *[see Warnings and Precautions]*.

Clinical Trials Experience

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

The safety data described in this section are based on a randomized, open-label clinical trial in patients with previously treated multiple myeloma. In this study, EMPLICITI 10 mg/kg was administered with lenalidomide and dexamethasone *[see Clinical Studies (14) in full Prescribing Information]*. For adverse reaction evaluation, EMPLICITI combined with lenalidomide and dexamethasone was compared with lenalidomide and dexamethasone alone.

The mean age of the population was 66 years and 57% of patients were 65 years of age or older. Sixty percent (60%) of the population were male, 84% were white, 10% were Asian, and 4% were black. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 47%, 1 in 44%, and 2 in 9% of patients.

These data reflect exposure of 318 patients to EMPLICITI and 317 to control with a median number of cycles of 19 for EMPLICITI and 14 for control.

Serious adverse reactions were reported in 65.4% of patients treated on the EMPLICITI arm and 56.5% for patients treated on the control arm. The most frequent serious adverse reactions in the EMPLICITI arm compared to the control arm were: pneumonia (15.4% vs. 11%), pyrexia (6.9% vs. 4.7%), respiratory tract infection (3.1% vs. 1.3%), anemia (2.8% vs. 1.9%), pulmonary embolism (3.1% vs. 2.5%), and acute renal failure (2.5% vs. 1.9%).

The proportion of patients who discontinued any component of the treatment regimen due to adverse reactions as listed below was similar for both treatment arms; 6.0% for patients treated on the EMPLICITI (elotuzumab) arm and 6.3% for patients treated on the control.

Adverse reactions occurring at a frequency of 10% or higher in the EMPLICITI arm and 5% or higher than the lenalidomide and dexamethasone arm for the randomized trial in multiple myeloma are presented in Table 1.

Table 1: Adverse Reactions with a 10% or Higher Incidence for EMPLICITI-Treated Patients and a 5% or Higher Incidence than Lenalidomide and Dexamethasone-Treated Patients [All Grades]

	EMPLICITI + Lenalidomide and Dexamethasone N=318		Lenalidomide and Dexamethasone N=317	
Primary Term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Fatigue*	61.6	12.6	51.7	11.7
Diarrhea	46.9	5.0	36.0	4.1
Pyrexia	37.4	2.5	24.6	2.8
Constipation	35.5	1.3	27.1	0.3
Cough†	34.3	0.3	18.9	0
Peripheral Neuropathy‡	26.7	3.8	20.8	2.2
Nasopharyngitis	24.5	0	19.2	0
Upper Respiratory Tract Infection	22.6	0.6	17.4	1.3
Decreased Appetite	20.8	1.6	12.6	1.3
Pneumonia§	20.1	14.2	14.2	9.5
Pain in Extremities	16.4	0.9	10.1	0.3
Headache	15.4	0.3	7.6	0.3
Vomiting	14.5	0.3	8.8	0.9
Weight Decreased	13.8	1.3	6.0	0
Lymphopenia	13.2	8.8	6.9	3.2
Cataracts	11.9	6.3	6.3	2.8
Oropharyngeal Pain	10.1	0	4.4	0

* The term fatigue is a grouping of the following terms: fatigue and asthenia.
† The term cough is a grouping of the following terms: cough, productive cough, and upper airway cough.
‡ The term peripheral neuropathy is a grouping of the following terms: peripheral neuropathy, axonal neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.
§ The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

Other clinically important adverse reactions reported in patients treated with EMPLICITI that did not meet the criteria for inclusion in Table 1 but occurred at a frequency of 5% or greater in the EMPLICITI group and at a frequency at least twice the control rate for the randomized trial in multiple myeloma are listed below:

General disorders and administration site conditions: chest pain

Immune system disorders: hypersensitivity

Nervous system disorders: hypoesthesia

Psychiatric disorders: mood altered

Skin and subcutaneous tissue disorders: night sweats

Laboratory abnormalities worsening from baseline and occurring at a frequency of 10% or higher in the EMPLICITI group and 5% or higher than the lenalidomide and dexamethasone group (criteria met for all Grades or Grade 3/4) for the randomized trial in multiple myeloma are presented in Table 2.

Table 2: Laboratory Abnormalities Worsening from Baseline and with a 10% or Higher Incidence for EMPLICITI-Treated Patients and a 5% Higher Incidence than Lenalidomide and Dexamethasone-Treated Patients [Criteria met for All Grades or Grade 3/4]

	EMPLICITI + Lenalidomide and Dexamethasone N=318		Lenalidomide and Dexamethasone N=317	
Laboratory Parameter	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Hematology				
Lymphopenia	99.4	76.7	98.4	48.7
Leukopenia	90.6	32.4	88.3	25.6
Thrombocytopenia	83.6	19.2	77.8	20.3
Liver and Renal Function Tests				
Hypoalbuminemia	73.3	3.9	65.6	2.3
Elevated Alkaline Phosphatase	38.7	1.3	29.8	0
Chemistry				
Hyperglycemia	89.3	17.0	85.4	10.2
Hypocalcemia	78.0	11.3	76.7	4.7
Low Bicarbonate	62.9	0.4	45.1	0
Hyperkalemia	32.1	6.6	22.2	1.6

Vital sign abnormalities were assessed by treatment arm for the randomized trial in multiple myeloma and are presented in Table 3. Percentages are based on patients who had at least one on-treatment vital sign abnormality any time during the course of therapy.

Table 3: Vital Sign Abnormalities

Vital Sign Parameter	EMPLICITI + Lenalidomide and Dexamethasone N=318 %	Lenalidomide and Dexamethasone N=317 %
Systolic Blood Pressure ≥160 mmHg	33.3	20.9
Diastolic Blood Pressure ≥100 mmHg	17.3	11.7
Systolic Blood Pressure <90 mmHg	28.9	8.2
Heart Rate ≥100 bpm	47.8	29.7
Heart Rate <60 bpm	66	31.3

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to EMPLICITI (elotuzumab).

Of 390 patients across four clinical studies who were treated with EMPLICITI and evaluable for the presence of anti-product antibodies, 72 patients (18.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. In 63 (88%) of these 72 patients, anti-product antibodies occurred within the first 2 months of the initiation of EMPLICITI treatment. Anti-product antibodies resolved by 2 to 4 months in 49 (78%) of these 63 patients. Neutralizing antibodies were detected in 19 of 299 patients in the randomized trial in multiple myeloma. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to EMPLICITI with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

Drug Interactions

No formal drug-drug interaction studies have been conducted with EMPLICITI. However, EMPLICITI is used in combination with lenalidomide and dexamethasone. Refer to the prescribing information for those products for important drug-drug interactions.

Laboratory Test Interference

EMPLICITI may be detected in the SPEP and serum immunofixation assays of myeloma patients and could interfere with correct response classification. A small peak in the early gamma region on SPEP that is IgGk on serum immunofixation may potentially be attributed to EMPLICITI, particularly in patients whose endogenous myeloma protein is IgA, IgM, IgD, or lambda light chain restricted. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no studies with EMPLICITI with pregnant women to inform any drug associated risks. Animal reproduction studies have not been conducted with elotuzumab.

EMPLICITI is administered in combination with lenalidomide and dexamethasone. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide and dexamethasone prescribing information for additional information. Lenalidomide is only available through a REMS program.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Lactation

Risk Summary

There is no information on the presence of EMPLICITI in human milk, the effect on the breast-fed infant, or the effect on milk production. Because of the potential for serious adverse reactions in breast-fed infants from elotuzumab administered with lenalidomide/dexamethasone, breastfeeding is not recommended. Refer to the lenalidomide and dexamethasone prescribing information for additional information.

Females and Males of Reproductive Potential

Pregnancy Testing

Refer to the lenalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

When EMPLICITI (elotuzumab) is used with lenalidomide, there is a risk of fetal harm, including severe life-threatening human birth defects associated with lenalidomide, and the need to follow requirements regarding pregnancy avoidance, including testing.

Contraception

Refer to the lenalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential and males.

Lenalidomide is present in the blood and semen of patients receiving the drug. Refer to the lenalidomide full prescribing information for requirements regarding contraception and the prohibitions against blood and/or sperm donation due to presence and transmission in blood and/or semen and for additional information.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 646 patients across treatment groups in the randomized trial in multiple myeloma, 57% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

The dose of EMPLICITI at which severe toxicity occurs is not known. EMPLICITI does not appear to be removed by dialysis as determined in a study of patients with renal impairment.

In case of overdosage, monitor patients closely for signs or symptoms of adverse reactions and institute appropriate symptomatic treatment.

PATIENT COUNSELING INFORMATION

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

Infusion Reactions

- EMPLICITI may cause infusion reactions. Advise patients to contact their healthcare provider if they experience signs and symptoms of infusion reactions, including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions]*.
- Advise patients that they will be required to take the following oral medications prior to EMPLICITI dosing to reduce the risk of infusion reaction *[see Dosage and Administration (2.2) in full Prescribing Information]*:
  - Dexamethasone orally as prescribed
  - H1 blocker: diphenhydramine or equivalent (if oral)
  - H2 blocker: ranitidine or equivalent (if oral)
  - Acetaminophen (650-1000 mg orally)

Pregnancy

- Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide is only available through a REMS program *[see Use in Specific Populations]*.

Infections

- Inform patients of the risk of developing infections during treatment with EMPLICITI, and to report any symptoms of infection *[see Warnings and Precautions]*.

Second Primary Malignancies

- Inform patients of the risk of developing SPM during treatment with EMPLICITI *[see Warnings and Precautions]*.

Hepatotoxicity

- Inform patients of the risk of hepatotoxicity during treatment with EMPLICITI and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

U.S. License No. 1713

1343639 Issued November 2015

689US1502988-04-01

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AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

SPECIAL ISSUE / ASH MEETING RECAP

JANUARY 2017
VOLUME 23 • ISSUE 1

Photo by © American Society of Hematology 2015

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

FROM THE CHAIRMAN

CAR-T Updates and Discussions on Improving Healthcare Delivery at the 2016 ASH Meeting

MIKE HENNESSY, SR

SCIENTISTS HAVE BEEN EXPLORING the use of chimeric antigen receptor (CAR) T cells in liquid tumors as a treatment option equivalent to the immune checkpoint inhibitors in solid tumors. However, there have been a few deaths associated with the use of CAR T-based treatments in patients with acute lymphoblastic leukemia that have been associated with cerebral edema in the patients—a side effect of the conditioning regimen.

These are, however, early stages of development for this treatment. Much remains to be understood—and there's a lot to look forward to, as well. Several presentations at the 58th annual meeting of the American Society of Hematology (ASH), held December 3-6, 2016, in San Diego, California, provided an update on advances being made with this treatment modality. While on the one hand, attendees were appraised on the latest clinical trial information for leukemias and lymphomas, a joint session by ASH and the European Hematology Association provided a realistic depiction of the progress made in the field of pluripotent stem cells (PSCs). One of the presenters was George Q. Daley, MD, director of the Stem Cell Transplantation Program, Boston Children's Hospital & Dana-Farber Cancer Institute. A veteran in the field of stem cell research, Daley's response to the question, "Will PSCs ever be therapeutically viable?" was a resounding "Yes!"

Sessions on healthcare quality at this year's meeting examined the importance of health information technology for both patients and providers. A lunch session hosted by the ASH Practice Partnership discussed the positive impact that the involvement of nurse practitioners and physician's assistants in care delivery can have on the healthcare system overall. Participants shared their experiences that documented not just improved time management by oncologists, but also cost savings and a better quality of life for the physicians—all without compromising on healthcare quality.

Unlike the last 2 years, where the ASH *Choosing Wisely*® Task Force reviewed *Choosing Wisely*® recommendations by ASH and other organizations, this year saw presentations by "Choosing Wisely Champions." These were practitioners who are working to eliminate costly and potentially harmful overuse of tests and procedures at their institutions. Their work was showcased during a special session at this year's meeting.

We hope you enjoy the conference coverage of ASH, which is the first special issue of *Evidence-Based Oncology*™ in 2017. For a current update on other clinical meetings and for healthcare news, please visit us at www.ajmc.com.

Sincerely,
Mike Hennessy, Sr
CHAIRMAN AND CEO

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

CAR-T Cells of Defined Composition Effective in Ibrutinib-Refractory CLL

Surabhi Dangi-Garimella, PhD

TURTLE

IN HIGH-RISK PATIENTS WITH chronic lymphocytic leukemia (CLL), CD19 chimeric antigen receptor (CAR)-T cells of defined composition can be administered with an acceptable early toxicity. This was the conclusion of a study presented by Cameron J Turtle, MBBS, PhD, University of Washington, Seattle, during an early morning session on the first day of the 58th American Society of Hematology Annual Meeting & Exposition.

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, causes partial responses (PRs) in a majority of patients with CLL. However, complete responses (CRs) are rare, and high-risk patients who progress on ibrutinib have short survival. Lymphodepletion chemotherapy followed by infusion of CD19-specific CAR-modified T cells has produced encouraging responses in CLL in phase 1 clinical trials, but the majority of patients in those studies had not previously received, or had failed, ibrutinib.

Describing the study population, Turtle showed that the study recruited 24 patients (median age 61 years; range, 40-73) who had received a median of 5 previous therapies (range, 3-9), including 4 patients who had failed prior allogeneic stem cell transplant. All 24 patients had previously been treated with ibrutinib—19 were ibrutinib-refractory, and 9 of these had a mutation in BTK or phospholipase gamma 2; 3 were ibrutinib-tolerant. Of the 24, 6 were venetoclax-refractory. Twenty-three patients had high-risk cytogenetics—16 had complex karyotype and 14 had a 17p deletion.

CRS GRADE	PATIENTS WITH CLL (N = 24)
0	4 (17%)
1	8 (33%)
2	10 (42%)
3	0 (0%)
4	1 (4%)
5	1 (4%)

CLL indicates chronic lymphocytic leukemia; CRS, cytokine release syndrome.

NT GRADE	PATIENTS WITH CLL (N = 24)
0	16 (67%)
1	0 (0%)
2	2 (8%)
3	5 (21%)
4	0 (0%)
5	1 (4%)

CLL indicates chronic lymphocytic leukemia; NT, neurotoxicity.

"We treated these 24 patients with CLL with anti-CD19 CAR-T cells that were manufactured from defined CD4+ and CD8+ T-cell subsets obtained by immunomagnetic selection of leukapheresis products," Turtle said. The cells were formulated in a final 1:1 ratio of $CD8^+$:$CD4^+$ CAR-T cells, and infused at 1 of 3 dose levels ($2x10^5$, $2x10^6$, or $2x10^7$ CAR-T cells/kg) after lymphodepletion chemotherapy.

At the time of data cut-off, 23 patients had completed response and toxicity assessment; 1 patient had died prior to restaging. "Analysis of all patients with B-cell malignancies treated with cyclophosphamide/fludarabine and CAR-T cells on our trial showed that the highest dose level ($2x10^7$ CAR-T cells/kg) was too toxic for an initial CAR T-cell infusion and identified a maximum tolerated first dose of $2x10^6$ CAR-T cells/kg," Turtle showed. The toxicities listed in the table above were observed in the study.

Turtle told the audience that 6 patients who received JCAR024 immunotherapy had to be treated with tocilizumab and dexamethasone for the cytokine release syndrome (CRS) and/or neurotoxic symptoms. Two of the 6 patients received vasopressors and needed care in the intensive care unit; 1 patient died due to cerebral edema.

Fourteen out of 17 patients who were bone marrow-negative for disease had immunoglobulin heavy (IGH) locus sequencing performed. The analysis found that the median progression-free survival was longer in IGHseq-negative versus IGHseq-positive patients.

CD19 CAR-T cells of defined CD4:CD8 ratio are highly active in CLL and can induce high response rates and durable CRs in poor prognosis patients who have previously failed ibrutinib. "We are working to discover serum biomarkers to identify how we can reduce neurotoxicity in patients who might be more susceptible and to provide an early intervention to prevent it," Turtle said.

He concluded his talk by saying that in high-risk CLL patients—defined as 17p deleted, with complex karyotype, ibrutinib-refractory, or venetoclax-refractory—CD19 CAR-T cells of defined composition, such as JCAR014, can be administered with an acceptable toxicity profile. Further, "Deep marrow clearance by IGHseq following JCAR014 provides early signs of durable responses with 100% progression-free survival and overall survival," Turtle said. ◆

REFERENCE

Turtle CJ, Hanafi L, Li D, et al. CD19 CAR-T cells are highly effective in ibrutinib-refractory CLL. Presented at: 58th American Society of Hematology Annual Meeting & Exposition; December 3, 2016; San Diego, CA. Abstract 56.

ADDITIONAL RESOURCES

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Cytokine Biomarkers Can Predict Response to CAR T-Cell Treatment in CLL

Surabhi Dangi-Garimella, PhD

MELENHORST

IMMUNOTHERAPY PRESENTS GREAT PROMISE as an anticancer therapy. While checkpoint inhibitors, such as nivolumab, pembrolizumab, and atezolizumab, continue to improve outcomes in several different tumor types, their limitation is the small number of patients who actually show a robust response to the drugs. A more personalized approach is the use of modified chimeric antigen receptor (CAR)-T cells, where the patient's own blood cells are modified to generate a more robust immune response against cancer cells.

At the 58th American Society of Hematology Annual Meeting & Exposition, held December 3-6, 2016, in San Diego, California, Jan Joseph Melenhorst, PhD, presented results of a study evaluating biomarkers of response to anti-CD19 CAR T-cell treatment in patients diagnosed with chronic lymphocytic leukemia (CLL). For this study, Melenhorst, adjunct associate professor of pathology and laboratory medicine, Center for Cellular Immunotherapies, Perelman School of Medicine at the University of Pennsylvania, collaborated with David L. Porter, MD, and Carl June, MD, who are pioneers in CAR T-cell research.

"While targeted therapies have shown remarkable activity in CLL, they are not curative," Melenhorst said. Stating that both extrinsic and intrinsic factors could influence CAR T-cell dysfunction in CLL, Melenhorst said that their group aimed to identify biomarkers in pre-manufacturing T cells and in the final product following expansion ex vivo.

The adoptive transfer of CTL019—formerly CART-19 cells—has shown remarkable activity and is known to induce long-term remissions in a subset of patients with relapsed/refractory CLL who typically have a poor prognosis. However, very

little is known about predictive indicators of efficacy with this treatment. The authors designed the present study to evaluate biomarkers of clinical response to CTL019 in CLL.

The study recruited 41 patients with advanced, heavily pretreated and high-risk CLL who received at least 1 dose of CTL019 cells. In vivo expansion and persistence were key quality attributes of CTL019 cells in patients with CLL who have complete responses to therapy, according to the authors. Melenhorst showed that responses were sustained beyond 5 years in 2 patients, accompanied by the persistence of functional CTL019 cells. The authors also identified transcriptomic signatures of early memory T cells that were associated with durable remissions, while T cells from nonresponding patients had higher expression of genes that regulate terminal differentiation and exhaustion.

"We saw a dramatically different proliferation potential of T cells in responders versus nonresponders," Melenhorst said. "In vitro proliferation correlated significantly with in vivo expansion, indicating that an intrinsic factor was associated with the proliferative capacity of these cells."

He added that transcriptional profile by cluster analysis indicated very distinct signatures, particularly with respect to early memory cells and exhaustion signature. T cells from nonresponders were enriched in genes belonging to known pathways of exhaustion. Additionally, early lineage T cells, Melenhorst showed, may mediate superior antitumor activity due to enhanced proliferation and survival following adoptive transfer.

Infused CAR-T cells in nonresponders also had reduced CD27 expression. "The combined assessment of PD1 and CD27 expression on CD8+ CTL019 cells in the infusion product accurately predicted response to treatment," Melenhorst said. He added that immune checkpoint inhibitor-directed combination therapy may reinvigorate CTL109 cells.

"Our gene analysis also showed the involvement of the STAT3 pathway," he stated, showing that CTL019 cells from complete responders secreted significantly higher levels of several cytokines, including CCL20, IL-21, IL-22, IL-17, and IL-6, indicating that the STAT3 signaling pathway may play a very important role in stimulating the enhanced potency of CTL019 cells.

"These data and additional immunological biomarkers may be used to identify which patients are most likely to respond to adoptive transfer strategies, leading to an enhanced personalized approach to cellular therapy," Melenhorst concluded. ◆

REFERENCE

Fraietta JA, Lacey SF, Wilcox NS, et al. Biomarkers of response to anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in patients with chronic lymphocytic leukemia. Presented at: the 58th American Society of Hematology Annual Meeting & Exposition; December 3, 2016; San Diego, CA. Abstract 57.

Phase 3 LyMa Trial: Rituximab After ASCT Increases OS in Mantle Cell Lymphoma

Surabhi Dangi-Garimella, PhD

LE GOUILL

MINIMAL RESIDUAL DISEASE is a major cause of relapse in patients treated for mantle cell lymphoma (MCL), which is a less common form of non-Hodgkin's lymphoma. While maintenance therapy with rituximab (RM) following R-CHOP (rituximab, cyclophosphamide, doxorubicin, hydrochloride, vincristine sulphate, and prednisone) has been shown to improve overall survival (OS) in older patients, its impact on OS in young patients following autologous stem cell transplant (ASCT) has not yet been evaluated.

Now, phase 3 results from the LyMa trial have shown that RM after ASCT prolongs event-free survival (EFS), progression-free survival (PFS), and OS in previously untreated young patients with MCL following ASCT. The results were presented during a session, Therapeutic Approach to Mantle Cell Lymphoma, by Steven Le Gouill, MD, PhD, from the Department of Hematology, Nantes University Hospital and UMR892 INSERM, of Nantes, France, at the 58th American Society of Hematology Annual Meeting & Exposition, held December 3-6, in San Diego, California. Le Gouill said that this was the first time that the final results of the LyMa trial were being shared.

Between September 2008 and August 2012, the trial enrolled 299 treatment-naïve individuals diagnosed with MCL. Inclusion criteria included diagnosis of MCL, presence of the t(11;14) translocation, untreated patients with MCL with at least 1 tumor site for assessment, aged between 18 and 65 years, and informed consent to participate in the trial. Patients were excluded from participation if they were diagnosed with another type of lymphoma besides MCL, if they were in relapse, positive for HIV or hepatitis B or C, or had uncontrolled diabetes.

THE 4-YEAR PROGESSION-FREE SURVIVAL WAS 67.8% AND OVERALL SURVIVAL WAS 78%.

Induction immuno-chemotherapy consisted of 4 courses of R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and salt platinum) every 21 days, followed by ASCT consolidation. Of the 277 patients who received 4 courses of R-DHAP and 20 who received R-CHOP, 257 underwent ASCT. Patients who did not respond after R-DHAP received 4 additional courses of R-CHOP-14 before ASCT (n = 20). The conditioning regimen for ASCT was R-BEAM (rituximab, BICNU, etoposide, ara-C, and melphalan). Patients who responded to ASCT were randomized to receive RM (1 infusion of 375 mg/m2 every 2 months for 3 years) or not (120 in each cohort).

Of the 257 patients who responded to ASCT, 240 were then randomized (1:1) to receive RM or not. The median follow-up was 54.4 months after inclusion (range, 52.7-59.2) and 50.2 months after randomization (range, 46.5-54.2). The primary endpoint was EFS, calculated from the time of randomization, with events defined as disease progression, relapse, death, severe infection, or allergy to rituximab. Secondary endpoints were PFS and OS from time of diagnosis and time of randomization.

The 4-year PFS was 67.8% (95% CI, 62.1%-72.8%) and OS was 78% (95% CI; 72.8-82.3). According to the EFS definition, 47 (39.2%) patients had an event in the no RM versus 25 (20.8%) in the RM arm. The median EFS from randomization was not reached in either arm. The 4-year EFS was 61.4% (95% CI, 51.3%-69.9%) in the no RM arm versus 78.9% (95% CI, 69.6%-85.6%) in the RM arm ($P = .0012$). The EFS duration was significantly superior in the RM arm, with a 54.3% reduction in the risk of event (HR, .457; 95% CI, 0.28-0.74; $P = .0016$). The median PFS and OS from randomization were not reached in both arms. The 4-year PFS from randomization was higher in the RM arm: 82.2% (95% CI, 73.2%-88.4%) versus 64.6% (95% CI, 54.6%-73%; $P = .0005$), as was the 4-year OS: 88.7% (95% CI, 80.7-93.5) versus 81.4% (95% CI, 72.3%-87.7%; $P = .0413$). Patients in the RM arm had a 60% reduction of risk of progression (HR, 0.4; 95% CI, 0.23%-0.68%; $P = .0007$) and a 50% reduction in risk of death (HR, 0.5; 95% CI, 0.25-0.98; $P = .0454$).

Based on their trial results, Le Gouill concluded, "A rituximab maintenance dose of 375 mg/m^2 every 2 months for 3 years is recommended in transplanted MCL patients." ◆

REFERENCE

Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab maintenance after ASCT prolongs survival in younger patients with mantle cell: phase 3 LyMa trial of the Lysa/Goelams group. Presented at: 58th American Society of Hematology Annual Meeting & Exposition; December 3, 2016; San Diego, CA. Abstract 145.

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

MAKE IMBRUVICA® YOUR FIRST STEP

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

CLL
SLL

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

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

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

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

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

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

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

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

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RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3]
Patients with 17p deletion were not included in the RESONATE™-2 trial[3]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

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

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

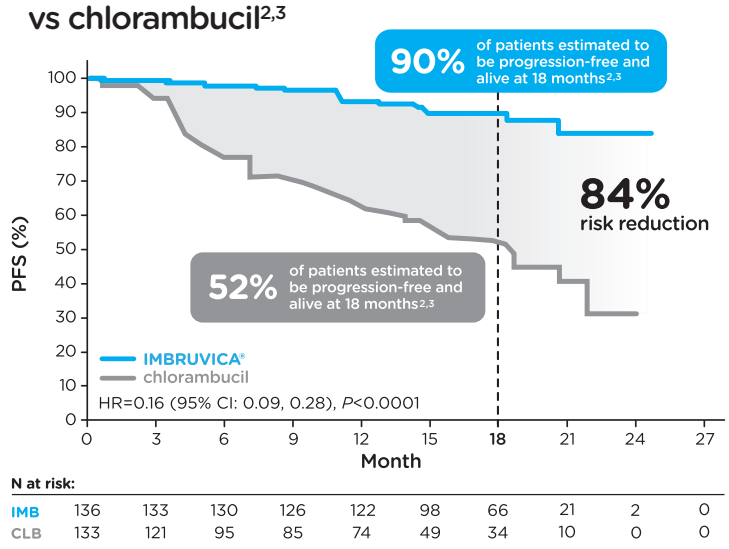
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

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



PRIMARY ENDPOINT: PFS

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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

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

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2016. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

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

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

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

* Based on laboratory measurements and adverse reactions

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

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

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

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

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

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 2

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

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

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

* Based on laboratory measurements per IWCLL criteria.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0

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

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

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

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

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

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

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

Waldenström's Macroglobulinemia: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial that included 63 patients with previously treated WM.

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

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

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

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

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

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

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

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

* Based on laboratory measurements.

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

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

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

Hepatobiliary disorders: hepatic failure (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

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

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

DRUG INTERACTIONS

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

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

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

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

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data]*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

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

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

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

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

Contraception:

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

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

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

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

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh class B and C) *[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]*.
- *Atrial fibrillation:* 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 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 capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions]*.
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*

Early Results Show Palbociclib Helps Sustain Patient Response to Ibrutinib in MCL

Surabhi Dangi-Garimella, PhD


MARTIN

WHILE IBRUTINIB AS A SINGLE AGENT is not very effective in maintaining a durable response in patients with mantle cell lymphoma (MCL), early phase 1 results now show that including the cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib in the treatment plan can help overcome resistance to ibrutinib. The results were presented by Peter Martin, MD, associate professor of medicine at Weill Cornell Medical College, Cornell University, during the 58th American Society of Hematology Annual Meeting & Exposition, held December 3-6, in San Diego, California.

"About one-third of patients on ibrutinib do not respond to the drug, and so combination treatments are warranted," Martin said. Previous studies by our group—in cell lines expressing wild-type Bruton's tyrosine kinase (BTK) and in primary human samples—showed that treatment with the G1-specific CDK4/6 inhibitor palbociclib can overcome ibrutinib resistance,[1] Martin told the audience. "We found that prolonged cell-cycle arrest could sensitize cells to death by a PI3K or BTK inhibitor."

The current phase 1 trial was designed based on the in vitro observations to evaluate the safety and preliminary activity of palbociclib plus ibrutinib in patients with previously treated MCL.[2] The primary objective of the trial was to select the recommended phase 2 dose for the combination of ibrutinib and palbociclib, with secondary objectives of characterizing the toxicity profile and estimating the objective response rate (ORR), the complete response (CR), and progression-free survival (PFS).

The primary eligibility criteria for trial enrollment, Martin said, were adults who were previously treated for MCL without receiving treatment with CDK4/6 or BTK inhibitors. Further, patients should have had acceptable marrow and organ function. The median age of the 23 enrolled patients was 65 years (range, 42-81), and a majority were male. Fourteen of the 23 had received prior autologous stem cell transplant.

TABLE. 1 Doses of Ibrutinib and Palbociclib Administered to Patients in the Trial

DOSE LEVEL	IBRUTINIB (DAILY)	PALBOCICLIB (DAYS 1-21/28)
1	280 mg	75 mg
2	420 mg	75 mg
3	420 mg	100 mg
4	580 mg	100 mg
5	580 mg	125 mg

Patients were treated in 28 day cycles—ibrutinib was administered daily and palbociclib was administered on days 1-21 (Table 1), and treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients were evaluated for efficacy at the end of cycles 3 and 6, and every 6 cycles, thereafter. Computed tomography (CT) was used to monitor patient response to treatment and confirmed by positron emission tomography/CT.

Table 2 lists the toxicities that were observed. Two patients experienced grade 3 rash at dose level 5 and were the only ones who required dose reductions; 6 patients required dose interruptions. Thirteen patients continued participating in the trial, while 4 dropped out due to disease progression, 2 due to adverse events, and 1 to undergo allogeneic stem cell transplantation. Dose-limiting toxicities established dose level 4 (ibrutinib 560 mg daily and palbociclib 100 mg x 21/28 days) as the maximum tolerated dose for further studies, Martin said.

TABLE 2. Treatment-associated Toxicities

GRADE	TOXICITY
3/4 hematological toxicity	Thromocytopenia (28%) Neutropenia (22%) Lymphopenia (17%)
3/4 nonhematological toxicity	Lung infection Encephalitis Hyponatremia Sinus tachycardia Pneumonitis Increased ALT/AST
1/2 adverse events	Diarrhea (50%) Fatigue (44%) Rash (39%) Bruising (17%) Nausea (17%) Fever (11%) Dyspepsia (11%) Myalgia (11%)

ALT indicates alanine transaminase; AST, aspartate transaminase.

Overall, 19 of 21 patients had a response to treatment, with 9 achieving a CR: 3 at dose level 1, 1 at dose level 2, and 2 at dose level 3. A partial response was observed in 4 patients, 1 each at doses levels 2 and 4 and 2 at dose level 3.

The ORR was 64% and the CR rate was 43%, with a median time to CR of 3 months. The estimated 1-year PFS was 61% and only 1 patient had disease progression.

Martin concluded that the mechanism-based combination of ibrutinib plus palbociclib was well tolerated in their study and showed activity. Biomarker studies to evaluate mechanisms of primary resistance are ongoing, and a phase 2 multicenter study to evaluate time to progression is planned, he added. "As is usually seen, patients whose disease progresses seem to do so early, and when they progress, they have poorer outcomes." ◆

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2. Martin P, Blum K, Bartlett NL, et al. A phase I trial of ibrutinib plus palbociclib in patients with previously treated mantle cell lymphoma. Presented at: 58th American Society of Hematology Annual Meeting & Exposition; December 3, 2016; San Diego, CA. Abstract 150.

RESONATE-2 Continues to Impress With Single-Agent Ibrutinib for CLL/SLL at 29 Months

Surabhi Dangi-Garimella, PhD

DESPITE THE COMPLEXITIES ASSOCIATED with treating older patients diagnosed with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), patients on the RESONATE-2 trial continue to present a favorable response to single-agent ibrutinib at a follow-up of 29 months. Paul Barr, MD, assistant professor of medicine, University of Rochester, Wilmot Cancer Institute, Rochester, New York, presented these results at the 58th American Society of Hematology Annual Meeting & Exposition, held December 3-6, in San Diego, California.

Barr told the audience that CLL/SLL are very common in older patients, who often have increased comorbidities and cannot tolerate aggressive treatments, which leads to poorer outcomes. Alkylating agents, such as chlorambucil, are a very common treatment option in this patient population. Ibrutinib is a Bruton's tyrosine kinase inhibitor, which was approved by the FDA in early 2016 as first-line treatment for CLL in patients who cannot tolerate strong treatment.[1] The approval was based on a little more than 18 months of follow-up of ibruti-

nib treatment; the current results are a 29-month follow-up.

Presenting the study design to the audience, Barr showed that 269 treatment-naïve patients diagnosed with CLL/SLL, who were at least 65 years old, were randomized 1:1 to either the chlorambucil or the ibrutinib arm. Patients with a 17p deletion were excluded from the study. Patients received 420 mg ibrutinib once daily until progression or chlorambucil 0.5 mg/kg on days 1 and 15 of a 28-day cycle, for up to 12 cycles. Patients continued on the study until study closure or disease progression. "Fifty-five patients on the chlorambucil arm were crossed over to the ibrutinib arm due to disease progression," Barr said.

"IBRUTINIB CONTINUES TO DEMONSTRATE OVERALL SURVIVAL BENEFIT OVER CHLORAMBUCIL."

- PAUL BARR, MD

The primary trial endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate, rate of hematologic improvement, and safety.[2]

Barr showed that ibrutinib prolonged PFS over chlorambucil, with an 88% reduction in risk of progression or death for patients randomized to ibrutinib. The 24-month PFS was 89% in the ibrutinib arm compared with 34% in the chlorambucil arm (P <.0001). PFS was significantly improved for ibrutinib across high-risk subgroups, including del11q and the unmutated *IGHV* gene, Barr showed.

"Ibrutinib continues to demonstrate OS benefit over chlorambucil," Barr said. The 24-month OS was 95% in the ibrutinib arm compared with 84% in the chlorambucil arm. "Complete response (CR) to ibrutinib continues to improve over time, increasing from 7% at 12 months to 15% at 24 months. At a median follow-up of 29 months, the CR rate is at 18%," Barr added.

Sustained improvements in hematological functions of patients were observed and were higher for ibrutinib compared with chlorambucil. In patients with anemia, hemoglobin levels were 90% versus 45% (P <.0001), ibrutinib versus chlorambucil, respectively. In patients with thrombocytopenia, platelet counts were at 80% versus 46% (P = .0055), ibrutinib versus chlorambucil, respectively.

"Ibrutinib is a good option because most patients remain on ibrutinib therapy at 29 months," Barr told the audience. He showed that 79% of patients have remained on ibrutinib, and 83% of participants continued on treatment for at least 2 years. Of the 21% patients who discontinued the drug:

- 3% had disease progression
- 12% had adverse events (AEs)
- 4% died
- 1% withdrew consent

In terms of AEs, atrial fibrillation was slightly higher (10%) than other studies, which could be because of the higher average age of this cohort, Barr explained. Of the 16 patients who discontinued ibrutinib treatment due to AEs, 13 remain alive after 13 months of follow-up. Some of the other AEs observed in the ibrutinib-treated arm included major hemorrhage, diarrhea, and anemia.

Ibrutinib is definitely more effective than chlorambucil in the high-risk patient population (del11q and unmutated *IGHV*), Barr said.

"The quality of responses in patients with CLL/SLL being treated with single-agent ibrutinib continues to improve with time," Barr concluded. "Further, rates of treatment-limiting AEs decreased over time, and a majority of the elderly patient population in the trial remains on daily ibrutinib." ◆

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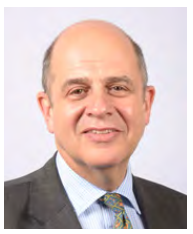
Phase 3 GALLIUM Study Shows Promising Results With Obinutuzumab for Follicular Lymphoma

Christina Mattina



MARCUS

RESULTS OF THE PHASE 3 GALLIUM STUDY, which compared the safety and efficacy of rituximab and obinutuzumab as first-line treatments for patients with previously untreated follicular lymphoma (FL), were presented at the 58th Annual Meeting & Exposition of the American Society of Hematology.

The research found that obinutuzumab-based immunochemotherapy and maintenance resulted in a significant improvement in progression-free survival (PFS) compared with rituximab therapy, supporting its use as a new standard of care for patients with FL despite a higher frequency of adverse events. The current standard of care for patients with advanced-stage FL is immunochemotherapy and maintenance with rituximab, which is associated with median PFS of 6 to 8 years and median survival of 12 to 15 years.

"Since the incorporation of rituximab into first-line therapy for patients with follicular lymphoma, the outlook for these patients has improved significantly. This is due, first, to the addition of rituximab to induction therapy, and secondly, as maintenance, with the PFS virtually double that seen a decade ago," said study author Robert Marcus, MA, FRCP, FRCPath, consultant hematologist at King's College Hospital in London. Despite these gains in survival time, patients frequently relapse after rituximab-based therapy for FL, which is incurable.

For this study, the researchers set out to examine the survival outcomes for treatment with obinutuzumab, which has shown promising activity and manageable toxicity when combined with chemotherapy in relapsed, indolent non-Hodgkin lymphoma. A total of 601 previously untreated patients with FL were assigned to receive the obinutuzumab chemotherapy regimen and 601 to receive rituximab. The primary endpoint was investigator-assessed PFS; the study also assessed safety and efficacy in the patients.

At a median follow-up time of 34.5 months, obinutuzumab-treated patients had a 34% reduction in the risk of progression or death. The observed hazard ratio of 0.66 for that treatment would translate to a 1.5-times longer median PFS compared with the rituximab arm, or an estimated 3-year increase in PFS if the rituximab arm had an assumed median PFS of 6 years. The rates of investigator-assessed PFS after 3 years were 80.0% for the obinutuzumab arm and 73.3% for the rituximab arm. At the time of the analysis, 5.5% of the patients receiving obinutuzumab and 8.7% of the patients receiving rituximab had died.

Though the obinutuzumab arm showed improvements in overall survival, these patients also reported adverse events (AEs) more frequently. In this group, 74.6% experienced grade 3 to 5 AEs and 46.1% reported serious AEs, compared with 67.8% and 39.9%, respectively, of rituximab patients. The AEs caused 16.3% of obinutuzumab patients and 14.2% of rituximab patients to discontinue treatment.

"Fewer patients are relapsing early, which may give this group more therapeutic options, and the complete remission rates with lower intensity regimens are increased with obinutuzumab, broadening the applicability of combination therapy to frailer patients," said Marcus. "We are optimistic that the early adoption of obinutuzumab-based therapy will further improve the outlook for patients with follicular lymphoma." ◆

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Ibrutinib Prevents Cytokine-Release Syndrome After CAR T-Cell Therapy for B-Cell Neoplasms

Christina Mattina

RUELLA

ALTHOUGH CHIMERIC ANTIGEN RECEPTOR (CAR)-T CELLS as a treatment for B-cell neoplasms have shown some promising results in clinical trials, their clinical use is limited, partially due to the risk of cytokine-release syndrome (CRS) occurring in response to the treatment. A poster presented at the Annual Meeting of the American Society of Hematology demonstrated that mice receiving CAR-T immunotherapy plus ibrutinib demonstrated longer overall survival and reduced cytokine production than the mice not treated with ibrutinib.[1]

"Cytokine-release syndrome is a serious adverse event of anti-CD19 chimeric antigen receptor T-cell (CART19) therapy and could potentially limit its widespread clinical use," explained lead study author Marco Ruella, MD, clinical instructor at the Perelman School of Medicine Center for Cellular Immunotherapies at the University of Pennsylvania. "In this preclinical study, we demonstrated that the [Bruton's tyrosine kinase]-inhibitor ibrutinib administered with CART19 can modulate cytokine production by CAR T cells and neoplastic B cells, therefore reducing CRS and increasing survival."

They created a human xenograft of CRS by infusing CART19 cells into mice that had a high B-cell tumor burden. The mice began to display signs of distress resembling CRS, including reduced mobility and hyperventilation, 2 days after the injection. Compared with the controls, CART19-treated mice showed significantly higher serum concentrations of several human cytokines. The researchers then tested their hypothesis that ibrutinib would reduce CART19-mediated CRS without impairing the anti-tumor efficacy of these cells.[2]

Ibrutinib, an inhibitor of Bruton's tyrosine kinase, has been approved as a first-line treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). It has been shown to modulate T-cell cytokine production, and the researchers recently demonstrated that its combination with CART19 leads to enhanced antitumor responses in preclinical models of MCL, CLL, and B-cell acute lymphoblastic leukemia.

To test their hypothesis, the researchers administered either a combination of CART19 plus ibrutinib or CART19 alone to mice with a high tumor burden of MCL. Mice treated with the ibrutinib combination demonstrated prolonged overall survival (median 17.5 days) compared with the mice that received the CART19 alone (median 5 days). Serum measurements 4 days after treatment showed that the ibrutinib-treated mice had significantly reduced cytokines, including IL-6, IFNγ, TNFα, IL-2, and GM-CSF.

"In vitro studies revealed that ibrutinib reduced cytokine production by CAR-T cells, as well as by MCL cells, leading us to postulate that both CRS and its successful prevention involve cross-talk between immune cells and cancer cells," the study authors wrote. They suggested that the CART19/ibrutinib combination "could be a novel strategy" in preventing CRS. ◆

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Prior Ibrutinib Treatment Improves CAR T-Cell Expansion, Could Impact Response in CLL

Surabhi Dangi-Garimella, PhD

CONCURRENT TREATMENT WITH THE Bruton's tyrosine kinase inhibitor, ibrutinib, improves expansion of chimeric antigen receptor (CAR)-T cells, and could subsequently improve response in patients with chronic lymphocytic leukemia (CLL). This was the conclusion drawn by Mark Blaine Geyer, MD, Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, as he presented the results of their study during the American Society of Hematology's annual meeting.

Ibrutinib, which has considerable efficacy as a single agent in patients with relapsed/refractory CLL, may modulate antitumor T-cell immune responses, Geyer told the audience, adding that studies have shown an enhanced ex vivo expansion of autologous T cells collected from patients treated with ibrutinib. This enhanced expansion following CD3/CD28 bead stimulation was also found to improve CD19-targeted CAR T-cell engraftment and antitumor efficacy in human xenograft models.[1] The study results presented by Geyer were from patients with CLL who were treated with ibrutinib at the time of autologous T-cell collection and/or around the time of CAR T-cell infusion enrolled in a phase 1 clinical trial of CD19-targeted CAR-T cells for adults with relapsed/refractory CLL or B-cell non-Hodgkin lymphoma.[2]

According to the study design shared by Geyer, 11 patients with CLL underwent leukapheresis followed by T-cell expansion and transduction. Patients were then evaluated for disease status and their peripheral blood and marrow samples were collected, followed by conditioning chemotherapy (2 to 7 days prior to the CAR T-cell infusion). Following the CAR T-cell infusion, peripheral blood samples were collected for postinfusion monitoring, including for cytokine response. "For the control group, we identified all evaluable ibrutinib-naïve patients with CLL treated on this study," Geyer told the audience.

Five patients (median age 58 years at CAR T-cell infusion) with relapsed/refractory CLL underwent therapy with ibrutinib at leukapheresis and/or immediately prior to or through conditioning chemotherapy (2 patients received cyclophosphamide and 3 received fludarabine) and CAR T-cell infusion; 6 additional evaluable patients with relapsed/refractory CLL remained ibrutinib-naïve through the conditioning regimen (4 received cyclophosphamide and 2 received bendamustine) and CAR T-cell infusion.

"We observed a nonsignificant trend toward greater median cumulative fold T-cell expansion ex vivo in the 5 patients on ibrutinib versus the 6 not on ibrutinib at leukapheresis," Geyer said, "with similar median manufacturing times of 13.5 versus 15 days [respectively]." According to data that Geyer shared, end-of-process T cells in patients treated with ibrutinib included a greater fraction of CD8+CAR+ T cells, with a CD62L+CD127+ phenotype, and decreased fraction of CD62L-negative T cells.

The **Table** indicates the toxicities that were documented in patients.

Ibrutinib-treated patients additionally exhibited greater median peak levels of multiple immunoregulatory cytokines associated with cytokine release syndrome, including IL-6, IL-10, IL-2, IL-5, IFNγ, FLT3L, fractalkine, and GM-CSF, Geyer told the audience.

Five of the 11 patients enrolled in the trial who were treated with conditioning chemotherapy and CAR-T cells achieved an objective response. The objective response rate (ORR) was 4/5 among ibrutinib-treated patients: 1 complete response (CR) without minimal residual disease (MRD), 1 MRD+ CR, and 2 partial responses ($P = .08$ for ORR between ibrutinib-treated vs ibrutinib-naïve patients). "Two patients remain in MRD-negative CR at 16 and 50 months, and they saw peak expansion between 7 and 14 days after CAR T-cell infusion," Geyer said, adding, "All 11 patients continue to survive."

Geyer concluded that while prior ibrutinib therapy improves autologous

TABLE. Toxicities Documented in Patients With CLL Infused With CAR-T Cells, With or Without Ibrutinib

CHARACTERISTIC	ALL PATIENTS (N = 11)	IBRUTINIB-EXPOSED (N = 5)	IBRUTINIB-NAÏVE (N = 6)
Fever (any):	11	5	6
On first day of CAR T-cell infusion	6	4	2
After first day of CAR T-cell infusion	5	1	4
Severe CRS:	2	2	0
Requiring tocilizumab	2	2	0
Requiring corticosteroids	1	1	0
Acute neurologic toxicity (any):	5	4	1
Grade 3	0	1	0
≥Grade 4	0	0	0

CAR indicates chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome.

T-cell expansion ex vivo and influence CAR T-cell phenotypes, it can amplify toxicities associated with CAR T-cell treatment, including CRS, based on differences in the conditioning therapy.

"Greater CAR T-cell expansion in vivo is an indicator of deeper clinical response," Geyer said. ◆

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How Soon Will Pluripotent Stem Cells Find Clinical Utility?

Surabhi Dangi-Garimella, PhD

DALEY

BRÜSTLE

AN AFTERNOON SESSION, hosted jointly by the American Society of Hematology (ASH) and the European Hematology Association (EHA) at the 58th Annual Meeting & Exposition of ASH, provided an update on a treatment that has been hailed as being promising for the medical field overall, not just oncology: pluripotent stem cells (PSCs).

The session was co-chaired by Charles S. Abrams, MD, president of ASH, professor of pathology and laboratory medicine, University of Pennsylvania Perelman School of Medicine, and Anthony R. Green, PhD, president of EHA, professor, Department of Hematology, Cambridge Institute for Medical Research, Wellcome Trust Medical Research Council Cambridge Stem Cell Institute.

PSCs, which are derived from the patient's own cells, are genetically matched with the recipient, which reduces the risk of treatment rejection. However, the process of generating these cells carries the risk of introducing new mutations and causing cancer. Will they ever be therapeutically viable?

According to George Q. Daley, MD, director of the Stem Cell Transplantation Program, Boston Children's Hospital and Dana-Farber Cancer Institute, Boston, the answer is a resounding "Yes!" A senior investigator who has been in the field of stem cell research for a very long time, Daley provided a background on stem cells. "PSCs are special because they can be maintained forever in culture, but can differentiate into any tissue in the human body," he said. First established in culture in 1998 by James Thompson, PhD, PSCs have already reached the clinic and a number of patients have been treated for diseases such as macular degeneration, while several clinical trials are evaluating this treatment for neurodegenerative diseases.

"In 2007, we perfected the process of reprogramming human stem cells. For any patient carrying a genetic disease, we can establish patient-derived PSCs. They can be manipulated in the laboratory using techniques such as CRISPR-Cas9 that can help gene repair of these PSCs," Daley said. He added that several blood-based diseases, including sickle cell disease, thalassemia, and Fanconi anemia can all be treated genetically.

"THE CLINICAL IMPACT OF INDUCED PLURIPOTENT STEM CELLS EXTENDS BEYOND STEM-CELL THERAPY AND CAN INFLUENCE CELL-BASED DRUG DISCOVERY AS WELL."

- OLIVER BRÜSTLE, MD

"We have embarked on using hematopoietic stem cells to replace defective platelets, red blood cells, and T cells, Daley added. "Disease models have already been developed for these." A long-term ambition of the field, he said, is to use PSCs to transfuse or engraft blood products, which will allow a predictable and pathogen-free resource of cells. A major challenge, however, is deriving the cell function, plus the costs associated with production and clinical work-up. These challenges evolve from the complex nature of mammalian blood lineage.

Daley then provided an update on how researchers are working to overcome these challenges, including the use of engineered T cells. Work by Themeli et al a few years back showed that tumor-targeted T cells, derived from induced PSCs (iPSCs), can be used in cancer treatment. The researchers combined iPSC and chimeric antigen receptor technology to generate human T cells targeted to CD19, an antigen expressed by malignant B cells, in tissue culture. These iPSC-derived T cells were able to inhibit tumor growth in a mouse model.[1] Daley ended his talk by emphasizing his belief in the clinical utility of iPSCs.

The second speaker at the session was Oliver Brüstle, MD, from the Institute of Reconstructive Neurobiology, University of Bonn, Bonn, Germany. Brüstle, a neuropathologist, is well renowned for his stem cell work in the field of neurobiology.

"With the nervous system, a major challenge is the lack of accessible donor tissue," Brüstle told the audience. The situation is further complicated by the fact that there is a "demographic tsunami," meaning neurodegenerative diseases are more common in older individuals, he said.

Brüstle provided the audience a flavor for the various potential applications of embryonic stem cells and iPSCs:

- Cell replacement in diseases, primarily affecting 1 neuronal subtype (eg, Parkinson's disease and Huntington's disease) and in disease affecting glial cells (eg, Pelizaeus-Merzbacher disease)
- Supportive/trophic effects
- Cell-mediated gene transfer
- Modifying tissue function such as in epilepsy

"With an increased knowledge on in vitro differentiation, PSC-based therapies for replacing distinct cell types has become palpable," Brüstle said. "The clinical impact of PSCs extends beyond stem-cell therapy and can influence cell-based drug discovery as well," he added. ◆

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ASH Symposium on Quality Addresses Health IT Challenges for the Provider and the Patient

Surabhi Dangi-Garimella, PhD

SINGH

BLAYNEY

HOWELL

Hardeep Singh, MD, is chief, Health Policy, Quality & Informatics Program, Michael E. DeBakey VA Medical Center.

Douglas W. Blayney, MD, is professor of Medicine, Stanford Cancer Institute, Stanford University.

Doris Howell, PhD, RN, is senior scientist, Princess Margaret Cancer Centre, Toronto, Ontario, Canada.

A KEY FINDING OF THE INSTITUTE OF MEDICINE

Committee on the Quality of Health Care in America's report, "Crossing the Quality Chasm: A New Health System for the 21st Century," published in March 2001,[1] was that information and communication technology is essential to improve quality of care. Subsequently, billions of dollars were invested to assist physicians, hospitals, and other healthcare settings in adopting health information technology (IT).

In the last decade, significant strides have been made to incorporate health IT into clinical practice. However, despite the emerging evidence of the impact of health IT on communication, healthcare quality, and efficiency, its impact on health-related outcomes is limited.

The Special Symposium on Quality at the 58th American Society of Hematology Annual Meeting & Exposition looked at how health IT can be utilized to improve healthcare quality, enhance patient–provider shared decision making, and facilitate efforts in quality research. Co-chaired by Anita Rajasekhar, MD, MS, Shands Hospital, University of Florida, and Vishal Kukreti, MD, Princess Margaret Cancer Centre, panelists included Hardeep Singh, MD, who heads the Health Policy, Quality & Informatics Program, Michael E. DeBakey VA Medical Center, Houston, Texas; Douglas W. Blayney, MD, Stanford Cancer Institute, Stanford University, Stanford, California; and Doris Howell, PhD, RN, Princess Margaret Cancer Centre, Toronto, Ontario, Canada.

Singh, who is also associate professor in the Department of Medicine, Baylor College of Medicine, Houston, Texas, posed the question, "Why is there disillusionment in health IT?" He pointed out that whereas health IT changes clinical practice, implementation of changes is often prone to failure. Quality and safety benefits need a while to implement, he said, and then there often are unintended consequences that we are not prepared for. "The bottom line is to ensure patient safety," Singh emphasized, adding that:

- Electronic health records (EHRs) must be safe.
- EHRs should be used safely, and episodes of reckless copy/paste should be avoided.
- EHRs should be used to improve safety.

Research conducted by Singh's group found that there are human errors involved at various stages of EHR use. He cited examples such as communication gaps because the physician did not read the nurse's notes, notes that are not accurate or are confusing, or wrong quality measures being implemented.

"Gaps in data and in communication result in data being lost in the bargain." Singh explained this with an example of how physicians might open an alert raised by the EHR system, but may not necessarily follow up on it. "Too many EHR alerts may lead doctors to miss them," Singh said. "We have had some initial success in the VA, and we are trying to prospectively use some algorithms to correct the situation."

Singh added that patients being engaged in their own care can significantly boost follow-up on their test results, and this can be achieved by sending patient data directly to patient portals. "However, the raw information might be difficult for patients to interpret."

Singh stressed that there is no single solution to the existing EHR troubles that our healthcare system is facing. "We need to address every dimension of the EHR problems," he said and provided the following solutions:

1. Software: need better tools/functions and designs for EHRs
2. Content: need smarter alerts and diagnostic decision support
3. Usability: need better user interfaces and to increase the signal:noise ratio
4. Workflow: needs improvement so there's time for physician–patient interaction
5. People: need patients and providers to be better engaged
6. Organization: need protocols for closed-loop test results follow-up
7. Evaluation and measurement: need to measure performance to ensure implementation and performance improvement
8. External influence: need to reimburse cognitive work

Blayney, who has presided over the American Society of Clinical Oncology, serves on the CancerLinQ Physician Advisory Committee. CancerLinQ is a big data platform that aggregates EHR data for quality benchmarking and to aid clinical decisions.[2] He addressed the challenges faced by providers in the clinic with using health IT platforms.

"Poor usability, mismanagement, and misidentification can all lead to HIT problems," Blayney said. "It's important to note that user interfaces need to be improved and people need to be trained as well." However, he emphasized that there needs to be an intuitive nature to using these interfaces, similar to using a mobile device, which is more user-friendly and intuitive.

Blayney explained that while electronic data capture shifts the data entry burden, it does not reduce the number of steps involved in assimilating all of that data. "At Stanford, we have taken advantage of the data warehouse to develop curated analytic data sets. So, the solution is to create access to data warehousing, use a curation engine, and create a documenting warehouse that can all help the process." He acknowledged, however, that all of this does not come cheap, that it needs significant monetary and personnel investment.

It's widely accepted, however, that without measurement, there is no improvement. Blayney provided an example of a breast cancer staging compliance report that was first sent to oncologists individually and then to entire groups to improve

physician adherence to the staging module. "By inserting a curation engine, we were able to add cancer stage as a measurable field," he said.

A team of experts at Stanford is also working on natural language processing to electronically extract data from clinical records.[3] "Capturing unplanned hospitalizations and emergency department visits as part of an episode of care, which might be happening outside of Stanford's network, is often difficult to capture." But the team developed a system to gather this information from EHRs, "Although a significant amount of curating was need, including for ambiguous terms like ER [estrogen receptor], PR [progesterone receptor], and other acronyms," Blayney told the audience. "It is important to reduce data mismanagement and to aggregate data across networks and nationally, and provide feedback to the physicians involved," he added.

Finally, Howell, who is a health services researcher, spoke about how health IT can enhance the patient experience. Patient engagement, she said, is about taking actions that help manage their health in order to benefit from healthcare. "It needs an active collaboration between patients and providers to design, manage, and achieve positive health outcomes," she added.

Studies have shown that actively engaging patients in their own care improves outcomes and encourages them to use more preventive services. They also experience better transitions between silos of care. Historically, the meaningful use criteria emphasized increased EHR use; however, the current belief is that empowering patients and improving their engagement with providers is more important for meaningful use.

Howell said that patients want to engage in technology to help improve their lives—such as appointment reminders, refills, etc. But do patients have the tools or equipment to care for themselves? Health IT can be used to support and empower patients via:

1. Education tools that provide patients access to their data
2. Data and information exchange among providers
3. Data and information exchange between providers and patients on symptom management and virtual treatments
4. Data and information exchange between providers and health systems

Howell told the audience that although health trackers/mobile health initiatives can help with early preventive intervention and to create a proactive model of care, issues, such as data capture and health privacy, remain. The bottom line is to think of the patient as a whole.

"Quality of life and patient experience is as important as the toxicities and adverse events that are documented," Howell said, adding that she is a firm believer in the potential of patient-reported outcomes measures. ◆

ADDITIONAL RESOURCES

Pharmacy Times

An overview of the optimal use of electronic health records by health system pharmacists

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ADDITIONAL RESOURCES

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Incorporating Nurse Specialists Into Hematology Care: Improved QOL for Patient and Provider

Surabhi Dangi-Garimella, PhD

ALVARNAS

ZUMBERG

KHOURY

HILL

Joseph Alvarnas, MD, is director, Value-Based Analytics and Clinical Quality for the Alpha Clinic for Cell Therapy and Innovation, City of Hope.

Marc Zumberg, MD, is professor of medicine and section chief, Benign Hematology, University of Florida.

H. Jean Khoury, MD, is professor and director, Division of Hematology, Department of Hematology and Medical Oncology, Winship Cancer Institute at Emory University.

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ON THE SECOND DAY of the 58th Annual Meeting & Exposition of the American Society of Hematology (ASH), Joseph Alvarnas, MD, chaired the ASH Practice Partnership lunch. Alvarnas, director of Value-Based Analytics and director of Clinical Quality for the Alpha Clinic for Cell Therapy and Innovation, City of Hope, Duarte, California, also serves as editor-in-chief of *Evidence-Based Oncology*™. The topic of discussion was the impact of including nurse practitioners (NPs), physician assistants (PAs), and clinical nurse specialists (CNSs) into hematology care.

As the care delivery model continues to evolve, the roles of NPs, PAs, and other CNSs who care for patients with hematologic diseases is growing. Although some practices work to ensure that these professionals come together as a team, many can be more efficient. For this particular session, Alvarnas was joined by Marc Zumberg, MD, professor of medicine and section chief, Benign Hematology, University of Florida, Gainesville, Florida; Clayton Hunter, PA-C, physician assistant, University of Florida, Gainesville, Florida; H. Jean Khoury, MD, professor and director, Division of Hematology, Department of Hematology and Medical Oncology, Winship Cancer Institute at Emory University, Atlanta, Georgia; and Brittany Hill, PA-C, MMSc, MSc, MPH, physician assistant, Department of Hematology and Medical Oncology, Winship Cancer Institute.

Zumberg shared best practices at their clinic at the University of Florida. "PA training is very exhaustive and rigorous, similar to an MD degree," he told the audience. "They have to maintain [continuing medical education] credits throughout their career. APRNs, or advanced practice registered nurses, [also] may have specializations, but they spend as much time as MDs, in the clinic," Zumberg said.

APs can improve patient access, support physicians in the clinic, and help physicians achieve a better work-life balance, according to Zumberg. "APs have prescribing privileges, and they can conduct patient visits. However, there could be some statewide differences," he said. Zumberg described 3 different models that can be used in practice:

1. Independent model, where the AP sees patients independently
2. Shared-visit model, where the patient is seen together with the physician
3. Mixed-visit model, which is a combination of the above

"A 50% increase in demand for oncologists is expected by 2020, but the number of oncologists is decreasing," Zumberg said. This is further complicated by the fact that there's been an 81% increase in survivors and those newly diagnosed with cancer, which demands a boost in the workforce.

Zumberg then shared the results of a study[1] initiated by the American Society of Clinical Oncology to conduct a national survey of integrating nonphysician practitioners (NPPs) and identifying collaborative practice models and services provided by NPPs. The study concluded that NPPs in oncology practices increase productivity for the practice and provide high physician and NPP satisfaction. Ninety-eight percent of patients were aware when care was provided by an NPP, and 92% reported being very satisfied with all aspects of the collaborative care that they received.

"I think incorporating APs is beneficial to the practice. It improves access to care, improves care continuity, and APs have a more holistic approach to patient care," Zumberg said, adding that physicians can benefit as well since they can now include more patients in the practice and reserve their time for the more complex patients. "Additionally, APs can improve the quality of life and work-life balance for MDs" he added.

Khoury described the model that is being practiced at the Winship Cancer Institute. "We have 70 APs at our clinic, and the model is patient- and caretaker-centered. The hematologist meets with new and complex patients, establishes and adapts treatment plans, and communicates changes to patients and the referring physician." The nurse coordinator, Khoury told the audience, has a very important role to play and is the main point of contact between the patient and the practice.

The AP functions independently and in parallel with the MD, implements and reinforces treatment plans, and flags events that require a physician intervention. "In addition to the AP, the care team includes a social worker, nurse coordinator, pharmacist, and the physician, of course," he added. "Our model is functional because we hold a pre-clinic meeting between the physician, the advance practice provider (APP), and the NP. The physician and APP have independent schedules—the physician develops a very clear care plan through notes, with the patient's expectations set at the first visit," said Khoury.

Hill described a typical APP schedule, which includes an average of 3 clinic days each week. "We also teach APP students, attend research meetings, and there's a continuing education clinic," she said. "Our in-patient model includes a team of 2 APPs in the hematology consult service." A very structured day is responsible for the model's successful implementation in the clinic, as is communication with the primary care team. "A similar model is followed in the inpatient leukemia and bone marrow transplant services," Hill added. Describing the integral role of the APP in the care team, she told the audience that the APP interacts with the patient and family members and holds end-of-life discussions as well.

Alvarnas asked the panelists, "As we think about value in healthcare, the theoretical construct of the triple aim, and creating a practical workflow, how do we blend them together?"

"A lot of these developments were associated with fellowship students and physician work hours," said Zumberg. "The traditional academic model of residency fellows was crumbling for us, so that when the APs came in, the institution saw an advantage in this. Over the years, the fellows have shifted their clinic time to cater to outpatient care and new consults."

"Taking on fresh students is a huge investment for physicians … they need to devote a significant amount of their time up front in training them," Hill said. "For me, personally, the learning curve was very steep during the first few months, but we continue to learn every single day." An important part of the process "is an open channel of communication between the AP and the physician," Hill emphasized. "There is need for flexibility and communication." ◆

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ASH "Choosing Wisely Champions" Share Their Practice-Changing Success

Surabhi Dangi-Garimella, PhD

IN COOPERATION WITH THE AMERICAN BOARD of Internal Medicine Foundation, the American Society of Hematology (ASH) introduced the "*Choosing Wisely* Champions" to recognize the efforts of practitioners who are working to eliminate costly and potentially harmful overuse of tests and procedures. These winners were invited to showcase their work at the 58th Annual Meeting & Exposition of ASH to provide attendees with an opportunity to learn and potentially implement these changes in their own practices. The session was chaired by Lisa K. Hicks, MD, oncological hematologist at St. Michael's Hospital, Toronto, Canada.

Ravindra Sarode, MD, medical director of clinical laboratory services, University of Texas Southwestern Medical Center, Dallas, Texas, spoke during the session, "Reduction in Unnecessary or Misapplied Thrombophilia Testing in Patients with DVT, PE, or Other Thrombotic Disorders Using Combination of Education and EMR Alerts. "The ASH *Choosing Wisely* guiding principles aim to reduce harm to patients, reduce costs, and are within the clinical domain of hematology," Sarode said. For his presentation, Sarode referred to recommendation 2 by ASH:

Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility).[1]

"Unfortunately, there are no thrombophilia-testing guidelines," he told the audience. "Why, whom, what, and when to test are always open-ended questions." Confusion over whether testing should be done in-house and the lack of testing guidelines in the adult and pediatric populations make for complicated decisions on testing.

Unnecessary testing can result in serious harm because of the following:

1. Testing is often conducted in provoked venous thromboembolism (VTE) during an acute event of anticoagulation
2. VTE testing often yields false-positive results
3. Testing often results in an unnecessary increase in healthcare costs

At their healthcare center, Sarode and his team analyzed consecutive thrombophilia testing orders during October and November of 2009, based on electronic health records (EHRs).[2] They evaluated indication, timing, comprehensiveness of tests, anticoagulation therapy at the time of testing, and confirmatory repeat testing, if any. Of the 173 patient records that were evaluated, a majority (72%) of patients were female.

- 70% had VTE or pregnancy loss (34%, unprovoked VTE or >3 pregnancy losses; 35%, provoked VTE; 31%, no documented reason)
- 51% were tested within 7 days of an index clinical event
- 51% were tested on anticoagulation therapy results affected by anticoagulation therapy
- 16% had a complete work-up with 1 work draw
- 84% had incomplete or fragmented testing, including unnecessary blood draws, which was a waste of time for the nurse and the technician
- 46% had abnormal results, and only 46% of these had abnormal tests repeated for confirmation; 54% potentially had a wrong diagnosis with long-term anticoagulation.

"We estimated a conservative loss of $1 million annually, over and above the incalculable loss of unnecessary long-term anticoagulation and related complications," Sarode said. "We implemented local guidelines for thrombophilia testing for clinicians, resulting in a reduction in healthcare costs and improved patient care. Twenty-two months after guideline implementation, a 92% reduction in testing was observed." However, the process was fraught with challenges, and communication was key, he acknowledged, which included verbal communication through meetings and grand rounds as well as changes within the Epic EHR system to flag testing each time it was ordered.

Maria I. Juarez, MD, from the Cancer Institute of Dallas, Mansfield, Texas, spoke during "Reduction of RBC Transfusion Via Updated Guidelines, Modified Workflow, and Physician Education." She detailed the project at their cancer institute that addressed recommendation 1 by ASH:

Don't transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, noncardiac in-patients).[1]

"Transfusions do not necessarily improve outcomes; rather, they can increase care costs and expose patients to unnecessary harm," Juarez said. "Our goal was to optimize PRBC, or packed red blood cell, utilization and develop a system-wide set of recommendations on the use of blood-based products."
The team then developed and shared system-wide guidelines on RBC transfusion. "Our intent was to modify the practice in the emergency department, with order sets configured for clinical decision support."

Their goal was to achieve a 20% reduction overall, and they ended up with a 27% reduction across the network. "Two hospitals within our network individually achieved a 35% reduction," she said.

Juarez told the audience that their project has been carried over as a system goal into 2017. "Guidelines have been developed for platelets, [fresh frozen plasma], and cryoprecipitate, and we hope to develop a system-analysis tool in parallel as well." The reason for our success was persistence, she emphasized.

The final presentation was by Javier Munoz, MD, Banner MD Anderson Cancer Center, Gilbert, Arizona, who spoke about their project during "Reduction of Post-Treatment Scanning Using EMR Alerts." This project stemmed from recommendation 5 by ASH:

Limit surveillance computed tomography (CT) scans in asymptomatic patients following curative-intent treatment for aggressive lymphoma.[1]

"Most patients with relapsed aggressive lymphomas are diagnosed outside of planned follow-up with scheduled imaging," Munoz said. "Imaging is costly and unnecessarily exposes asymptomatic patients to radiation, which builds up over time."

According to the National Comprehensive Cancer Network Guidelines, patients with stage 3 or 4 diffuse large B-cell lymphoma should undergo a CT scan every 6 months for 2 years and

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then yearly if needed, he said. Particularly for Hodgkin lymphoma, CT should not be done routinely because it can lead to false-positives, he added.

"To bring about this system and behavior change, our hypothesis was that a combination of provider education and automatic EHR alerts could stop physicians from sending a patient for unnecessary scans," Munoz said. Their team developed the following clinical practice statement: limit surveillance in asymptomatic patients with lymphoma. They engaged both providers and patients to raise awareness and implement changes, he said.

"Our preliminary results found that automatic alerts generated within the EHR may decrease imaging," Munoz said, adding, "Education is definitely important for the success of such system-wide projects." ◆

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American Society of Hematology's Tenets for Hematologists to Choose Wisely

Surabhi Dangi-Garimella, PhD

INITIATED BY THE AMERICAN BOARD OF INTERNAL MEDICINE, *Choosing Wisely*® is a campaign that has seen participation by a number of different national medical organizations to promote conversations between clinicians and patients to help them choose care that:

- Is evidence-based
- Does not duplicate other tests or procedures that the patient may have already received
- Does not harm the patient
- Is absolutely essential[1]

A task force appointed by the American Society of Hematology has developed 10 recommendations[2] for hematologists to be aware of and to follow:

1. *Don't transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, noncardiac in-patients).*
   Transfuse the smallest effective dose of RBCs, because liberal transfusion does not improve outcomes, could harm patients, and generates costs.

2. *Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).*
   Thrombophilia testing is costly and can harm patients; it does not change management of VTEs that occur in the setting of major transient risk factors. For complex cases, however, patients and clinicians should seek guidance from an expert in VTE.

3. *Don't use inferior vena cava (IVC) filters routinely in patients with acute VTE.*
   IVC filters can harm the patient and are costly. They are not recommended unless the patient has acute VTE and an anticoagulant is contraindicated. Retrievable filters are recommended over permanent filters for patients experiencing pulmonary embolism (PE), and they should be removed when the risk of PE has resolved.

4. *Don't administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e. outside of the setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).*
   Blood products can harm patients and are costly. They are not typically indicated for the reversal of vitamin K antagonists. '

5. *Limit surveillance computed tomography (CT) scans in asymptomatic patients following curative-intent treatment for aggressive lymphoma.*
   CT surveillance is expensive and does not improve survival in patients in remission from aggressive non-Hodgkin lymphoma. Moreover, they can increase the risk of radiation exposure. As the risk of relapse decreases with time, CT scans in asymptomatic patients who are at least 2 years beyond treatment completion is not advised.

6. *Don't treat with an anticoagulant for more than 3 months in a patient with a first venous thromboembolism (VTE) occurring in the setting of a major transient risk factor.*
   Patients with a first VTE triggered by a major, transient risk factor are at low risk of recurrence once the risk factor has resolved and an adequate treatment regimen with anticoagulation has been completed. An appropriate regimen of anticoagulation can avoid unnecessary harm, reduce health care expenses, and improve quality of life.

7. *Don't routinely transfuse patients with sickle cell disease (SCD) for chronic anemia or uncomplicated pain crisis without an appropriate clinical indication.*
   Patients with SCD are more vulnerable to harms of RBC transfusion, such as alloimmunization to minor blood group antigens and iron overload. Patients with SCD whose baseline hemoglobin (Hb) ranges between 7-10 g/dl can tolerate further reductions without symptoms of anemia. Intravenous drips in these patients can further decrease their Hb, and so routine transfusion in these patients is contraindicated.

8. *Don't perform baseline or routine surveillance CT scans in patients with asymptomatic, early-stage chronic lymphocytic leukemia (CLL).*
   In patients with asymptomatic, early-stage CLL, baseline and routine surveillance CT scans do not impact survival and are not important to stage or prognosticate patients. CT scans expose patients to unnecessary radiation and may not provide clinically relevant information—in addition to being expensive. Instead, clinical staging and blood monitoring should be performed.

9. *Don't test or treat for suspected heparin-induced thrombocytopenia (HIT) in patients with a low pretest probability of HIT.*
   The 4Ts score–thrombocytopenia, timing of platelet count, thrombosis or other sequelae, and other cause of thrombocytopenia—is recommended to calculate the pretest probability of HIT in patients suspected of HIT. Further investigation is not recommended if the pretest 4T score is low (between 0 and 3). Heparin should not be discontinued or non-heparin anticoagulant should not be initiated in these low-risk patients.

10. *Don't treat patients with immune thrombocytopenic purpura (ITP) in the absence of bleeding or a very low platelet count.*
    Treatment for ITP should prevent bleeding episodes and improve patient quality of life. Unnecessary treatment can be harmful and costly–so decisions to treat ITP should be based on an individual patient's symptoms, bleeding risk, social factors, side effects of possible treatments, upcoming procedures, and patient preferences. Unless an adult (platelet count greater than 30,000 µL) has to undergo surgery or other invasive procedures, or have a risk of bleeding, ITP is not indicated.

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Rubraca™ (rucaparib) tablets

Rubraca™ (rucaparib) is now FDA approved and available

The only FDA-approved PARP inhibitor indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca.[1]

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]

BRCA=BReast CAncer susceptibility gene.

Please visit Rubraca.com for more information

SELECT IMPORTANT SAFETY INFORMATION

There are no contraindications with Rubraca.

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

AML was reported in 2 (<1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1).

Monitor complete blood count testing at baseline and monthly thereafter. For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Rubraca can cause fetal harm when administered to pregnant women based on its mechanism of action and findings from animal studies. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Most common adverse reactions (≥ 20%; Grade 1-4) were nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), decreased appetite (39%), diarrhea (34%), abdominal pain (32%), dyspnea (21%), and thrombocytopenia (21%).

Most common laboratory abnormalities (≥ 35%; Grade 1-4) were increase in creatinine (92%), increase in alanine aminotransferase (ALT) (74%), increase in aspartate aminotransferase (AST) (73%), decrease in hemoglobin (67%), decrease in lymphocytes (45%), increase in cholesterol (40%), decrease in platelets (39%), and decrease in absolute neutrophil count (35%).

Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Clovis Oncology, Inc. at 1-844-258-7662.

Please see Brief Summary of Prescribing Information on adjacent pages.

Reference: 1. Rubraca [package insert]. Boulder, CO: Clovis Oncology; 2016.

CLOVIS ONCOLOGY

RUBRACA™ (rucaparib) tablets, for oral use

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Rubraca™ is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca *[see Dosage and Administration (2.1) in the full prescribing information]*.

This indication is approved under accelerated approval based on objective response rate and duration of response *[see Clinical Studies (14) in the full prescribing information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

In addition, AML was reported in 2 (< 1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Monitor complete blood count testing at baseline and monthly thereafter. Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the AUC in patients receiving the recommended dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions]*.

Clinical Trials Experience

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

Rubraca 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197).

Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). The median duration of treatment was 5.5 months (range 0.1 to 28.0).

Table 2 and Table 3 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with Rubraca.

Table 2. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily

	All Ovarian Cancer Patients (N = 377) %	
Adverse Reaction	**Grades[a] 1-4**	**Grades 3-4**
Gastrointestinal Disorders		
Nausea	77	5
Vomiting	46	4
Constipation	40	2
Diarrhea	34	2
Abdominal Pain	32	3
General Disorders		
Asthenia/Fatigue	77	11
Blood and Lymphatic System Disorders		
Anemia	44	25
Thrombocytopenia	21	5
Nervous System Disorders		
Dysgeusia	39	0.3
Metabolism and Nutrition Disorders		
Decreased appetite	39	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	21	0.5

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)

The following adverse reactions have been identified in < 20% of the 377 patients treated with Rubraca 600 mg twice daily: dizziness (17%), neutropenia (15%), rash (includes rash, rash erythematous, rash maculopapular and dermatitis) (13%), pyrexia (11%), photosensitivity reaction (10%), pruritus (includes pruritus and pruritus generalized) (9%), Palmar-plantar erythrodysaesthesia syndrome (2%), and febrile neutropenia (1%).

Table 3. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily

	All Patients with Ovarian Cancer (N = 377) %	
Laboratory Parameter	**Grade 1-4 [a]**	**Grade 3-4**
Clinical Chemistry		
Increase in creatinine	92	1
Increase in ALT[b]	74	13
Increase in AST[b]	73	5
Increase in cholesterol	40	2
Hematologic		
Decrease in hemoglobin	67	23
Decrease in lymphocytes	45	7
Decrease in platelets	39	6
Decrease in absolute neutrophil count	35	10

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.

[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. There are no available data in pregnant women to inform the drug-associated risk. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily *[see Data]*. Apprise pregnant women of the potential risk to a fetus.

The 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% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a dose range-finding embryo-fetal development study, pregnant rats received oral doses of 50, 150, 500, or 1000 mg/kg/day of rucaparib during the period of organogenesis. Post-implantation loss (100% early resorptions) was observed in all animals at doses greater than or equal to 50 mg/kg/day (with maternal systemic exposures approximately 0.04 times the human exposure at the recommended dose based on $AUC_{0\text{-}24h}$).

Lactation

Risk Summary

There is no information regarding the presence of rucaparib in human milk, or on its effects on milk production or the breast-fed infant. Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of Rubraca.

Pediatric Use

The safety and effectiveness of Rubraca in pediatric patients have not been established.

Geriatric Use

One hundred and sixty (42%) of the 377 ovarian cancer patients in clinical trials of Rubraca were 65 years of age or older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The effectiveness of Rubraca in patients with *BRCA*-mutant ovarian cancer who were 65 years of age or older could not be assessed due to the small number of patients (N=38).

Hepatic Impairment

No starting dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation of starting dose adjustment is available for patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) due to a lack of data *[See Clinical Pharmacology (12.3) in the full prescribing information]*.

Renal Impairment

No starting dose adjustment is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] between 30 and 89 mL/min, as estimated by the Cockcroft-Gault method). There is no recommended starting dose for patients with CLcr less than 30 mL/min or patients on dialysis due to a lack of data *[See Clinical Pharmacology (12.3) in the full prescribing information]*.

OVERDOSAGE

There is no specific treatment in the event of Rubraca overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION

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

MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. These may be signs of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Rubraca *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after receiving the last dose of Rubraca *[see Warnings and Precautions and Use in Specific Populations]*.

Photosensitivity: Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking Rubraca *[see Adverse Drug Reactions]*.

Lactation: Advise females not to breastfeed during treatment and for 2 weeks after the last dose of Rubraca *[see Use in Specific Populations]*.

Dosing Instructions: Instruct patients to take Rubraca orally twice daily with or without food. Doses should be taken approximately 12 hours apart. Advise patients that if a dose of Rubraca is missed or if the patient vomits after taking a dose of Rubraca, patients should not take an extra dose, but take the next dose at the regular time *[see Dosage and Administration (2.1) in the full prescribing information]*.

Distributed by:
Clovis Oncology, Inc.
Boulder, CO 80301
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Issued: December 2016
PP-RUCA-US-0252

Healthcare Costs and Utilization After First-Line Therapy for Medicare DLBCL Patients

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HUNTINGTON

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A COMPARISON OF MEDICARE claims for patients with diffuse large B-cell lymphoma (DLBCL) after first-line treatment found that the patients who relapsed had higher rates of healthcare utilization and greater costs than the patients who had not relapsed. The research, presented at the American Society of Hematology's 58th Annual Meeting & Exposition, suggests that improvements in first-line DLBCL therapy can offer "significant healthcare savings in addition to improved clinical outcomes."[1]

Recent study results on patients with non-Hodgkin lymphoma have indicated that the average costs for those on active treatment were $5871 per patient per month versus $355 for control patients during a 2-year follow-up period.[2] DLBCL, an aggressive subtype of non-Hodgkin's lymphoma, has relatively high rates of relapse after initial treatment, but there is limited research on treatment patterns post first-line therapy and the healthcare costs associated with relapses. As such, the study authors set out to measure healthcare utilization and costs after the completion of first-line DLBCL therapy.

The retrospective study was conducted by gathering Medicare claims data and selecting adults over age 65 who had received their first time DLBCL diagnosis between January 1, 2010, and June 30, 2014. The researchers created a study cohort of patients receiving post first-line therapy by defining the end of first-line treatment as a gap of over 60 days in therapy. The relapsed group consisted of beneficiaries who then initiated second-line therapy, while the nonrelapsed group was made up of individuals who completed the first-line therapy without receiving any other chemotherapy treatment.

"IMPROVEMENTS IN FIRST-LINE DLBCL TREATMENT THAT INCREASE DURABLE REMISSIONS ARE LIKELY TO OFFER SIGNIFICANT HEALTHCARE SAVINGS IN ADDITION TO IMPROVED CLINICAL OUTCOMES."

-Scott Huntington, MD, MPH, MSHP

Of the 5909 beneficiaries, 1552 had claims data for second-line therapy during the follow up period, while the remaining 4357 did not. The relapsed and nonrelapsed groups had similar mean ages and other baseline characteristics, although there were differences in first-line treatment between the 2 groups. The patients who had relapsed were more likely to have received rituximab monotherapy, bendamustine-rituximab, or CVP (cyclophosphamide, vincristine, and prednisone) regimens, while the nonrelapsed patients were more likely to have received R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for first-line therapy. Mean follow-up time after first-line therapy was similar between the 2 cohorts.

Analysis of the claims data found that the relapsed cohort had significantly higher healthcare utilization after first-line therapy compared with the nonrelapsed patients. The most pronounced difference was in rates of inpatient hospital admissions: the relapsed cohort had claims in 60.7% of cases compared with 41.1% of the nonrelapsed group. The relapsed group also had a mean of 37.93 follow-up outpatient visits per patient per year compared with 24.75 per patient per year in the nonrelapsed group. And the relapsed group had significantly higher rates of emergency department visits, Medicare Part D pharmacy claims, and use of skilled nursing facility, home health agency, and hospice services.

These increases in utilization were unsurprisingly linked to higher mean all-cause healthcare costs. The relapsed cohort was responsible for total healthcare costs of $4848 per patient per month, more than 3 times higher than the $1427 in costs among nonrelapsed patients. The major cost drivers of this disparity among the patients who had relapsed compared with the nonrelapsed group were total outpatient care ($2984 vs $632) and inpatient costs ($1220 vs $443). Among relapsed patients, the total costs from the date of relapse to the end of the study were double the costs during remission. In addition to limitations of assessing claims data, the authors indicate that 1674 patients who died within 12 months of index data were excluded from the study, which included 29.8% of patients in the relapsed cohort and 21.4% in the nonrelapsed cohort.

"Our study confirms healthcare utilization is significantly higher in older adults who progress after first-line therapy for DLBCL compared to those without disease relapse," said lead study author Scott Huntington, MD, MPH, MSHP, assistant professor at Yale University School of Medicine's Section of Hematology, in an e-mail response to *Evidence-Based Oncology*™. "Thus, improvements in first-line DLBCL treatment that increase durable remissions are likely to offer significant healthcare savings in addition to improved clinical outcomes. These findings may be particularly helpful for informing value-based drug pricing in the future." ◆

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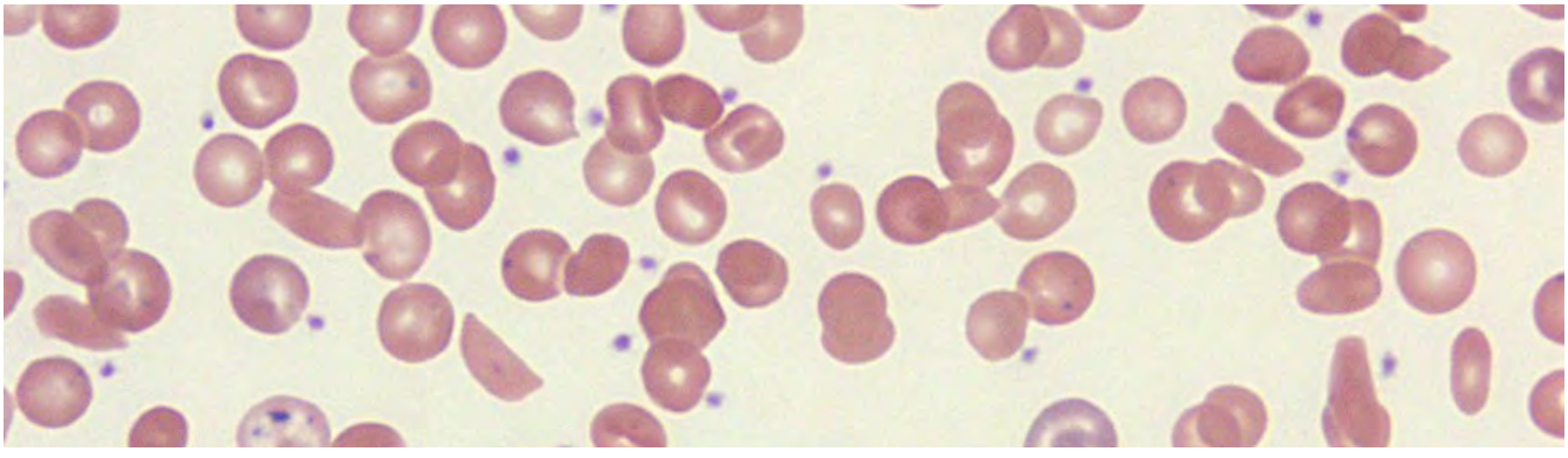

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Model to Predict Disease Complexity and Costs Associated With AHCT in Acute Leukemia

Surabhi Dangi-Garimella, PhD

"VALUE," BY ITS TRADITIONAL DEFINITION, is denoted as the ratio of outcomes over cost. With the transition across healthcare toward value-based payments, payers—both CMS and commercial payers—are experimenting with payment models that will yield the best healthcare outcomes at lower costs. For acute leukemia (AL), while risk-based survival outcomes have been reported for allogenic hematopoietic cell transplant (AHCT), associated financial risk has not been assessed.

A poster presented at the 58th Annual Meeting & Exposition of the American Society of Hematology reported on a risk-based cost analysis model in patients with AL that considered the impact of disease status, patient comorbidities, AHCT donor type, and other transplant-related factors on clinical and financial risks. The presenting author of the poster was Joseph C. Alvarnas, MD, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, California. Alvarnas also serves as editor-in-chief of *Evidence-Based Oncology*™.

The study included data from multiple sources of electronic health records (EHRs) of patients with AL who underwent AHCT at City of Hope during a 4-year period between January 2010 and December 2014. Total direct costs were assessed for each patient from 14-days prior to 100-days post AHCT. The 389 patients included in the analysis had a median age of 52.5 years (range, 1-74 years) and just less than half (48%) were female.

At the time of AHCT, 204 (52%) were in first complete remission (CR), 87 (22%) in first relapse/second CR, and 98 (25%) were in their third or more CR/induction failure (IF). In addition, 214 (55%) patients received a myeloablative conditioning regimen, 175 (45%) received a reduced-intensity conditioning regimen, and 231 (59%) had matched unrelated donor (MUD) or mismatched related donor (MRD) AHCT. A majority (80%) of patients received a graft-versus-host disease (GVHD) prophylactic regimen of tacrolimus/sirolimus. In terms of health coverage for this treatment, 207 patients were enrolled on a therapeutic intervention trial and 121 had Medicare and/or Medicaid (Medi-Cal).

At a median follow-up of 13 months (range, <1-62 months), the estimated 1-year unadjusted overall survival (OS) for the entire group post-AHCT was 71% (95% CI, 66%-75%); for patients in first CR, 80% (95% CI, 74%-85%); for patients in first relapse/second CR, 68% (95% CI, 57%-77%); and for patients who had their third or higher CR/IF, 56% (45%-65%). One-year OS was similar for sibling-matched (73%) and MUD/MRD (70%) transplants.

A multivariable analysis by the authors demonstrated that disease status, MUD/MRD donor, myeloablative conditioning regimen, GVHD prophylaxis other than tacrolimus/sirolimus, and Medicare and/or Medicaid as payer were significant predictors for cost of care to be more than the median. Using the Akaike Information Criterion scores, the authors showed that donor type and disease status at AHCT were more informative variables with regard to higher cost of AHCT.

Disease status, MUD/MRD, myeloablative conditioning regimen, Medicare and/or Medicaid as payer also were significant predictors of cost in the 80th percentile or greater, the authors found. Notably, despite reaching statistical significance in univariate analysis age, cytogenetics, treatment on protocol, and Sorrer score lost significance in adjusted higher costs and OS multivariate models.

Based on their analysis, the authors concluded:

- Patients with more advanced disease status and inferior performance status drive higher costs, as do higher levels of care complexity
- Statistically significant drivers of higher care costs can be predicted prior to AHCT using EHR data.

"While validation of this model is necessary using large payer or multi-institutional databases, we propose that similar clinical–economic models can be created for patients with other blood cancers who requiring high complexity care," Alvarnas told *Evidence-Based Oncology*™. ◆

ALVARNAS

Joseph C. Alvarnas, MD, is director, Value-Based Analytics and Clinical Quality for the Alpha Clinic for Cell Therapy and Innovation, City of Hope.

REFERENCE

Alvarnas JC, Marcucci G, Vanderplas A, et al. A multivariate clinical and economic model for predicting risk-based costs of care for acute leukemia (AL) patients (pts) undergoing allogeneic hematopoietic cell transplant (HCT). Presented at: 58th American Society of Hematology Annual Meeting & Exposition; December 4, 2016; San Diego, CA. Abstract 3547.

COST OF CARE

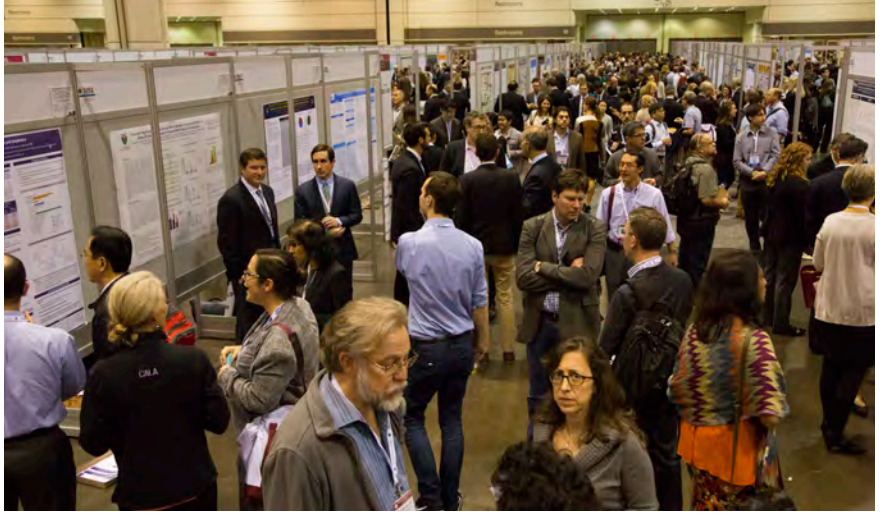
Healthcare Utilization and Costs Associated With the Treatment of Relapsed/Refractory MM

Surabhi Dangi-Garimella, PhD

A POSTER PRESENTED on the second day of the 58th Annual Meeting & Exposition of the American Society of Hematology compared the utilization patterns and associated costs for recently approved and older drugs in patients with relapsed/refractory multiple myeloma (rrMM) in the United States. The results can help inform future economic evaluations for these drugs. »

Using data from the Truven Health MarketScan Commercial and Medicare Database, the study retrospectively evaluated the utilization of carfilzomib (Kyprolis), pomalidomide (Pomalyst), and panobinostat (Farydak) for the treatment of patients with rrMM following failure of at least 2 prior standard therapies. Patients (older than 18 years) who were diagnosed with MM between January 1, 2006, and May 31, 2015, were included in the study if they had not undergone stem cell transplant and had been continuously enrolled in treatment at least 6 months before and at least 1 month after their first diagnosis of MM and treatment initiation. For the healthcare resource utilization and cost analysis, the authors included only those patients who had at least 6 months of continuous enrollment after treatment initiation.

If 2 or more drugs were started within 90 days, they were considered a single regimen. A treatment gap of at least 90 days or introduction of a new treatment, whichever occurred first, defined the end of a line of treatment (LOT). Time to next treatment (TTNT) »



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SUSTOL® (granisetron) extended-release injection, for subcutaneous use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
SUSTOL is a serotonin-3 (5-HT3) receptor antagonist indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

DOSAGE AND ADMINISTRATION
Administration: For subcutaneous injection only, SUSTOL is intended for administration by a healthcare provider. Administer SUSTOL in the skin of the back of the upper arm or in the skin of the abdomen, at least 1 inch away from the umbilicus. Do not administer anywhere the skin is burned, hardened, inflamed, swollen, or otherwise compromised. Due to the viscosity of SUSTOL, administration requires a slow, sustained injection over 20 to 30 seconds.

Recommended Dosage: The recommended dosage of SUSTOL in adults is 10 mg administered as a single subcutaneous injection at least 30 minutes before the start of emetogenic chemotherapy on Day 1. Do not administer SUSTOL more frequently than once every 7 days. Use of SUSTOL with successive emetogenic chemotherapy cycles for more than 6 months is not recommended. See full prescribing information for recommended dosage of concomitant dexamethasone.

Renal Impairment: In patients with moderate renal impairment (ClCr 30-59 mL/min), administer SUSTOL not more frequently than once every 14 days. Avoid SUSTOL in patients with severe renal impairment (ClCr <30 mL/min).

DOSAGE FORMS AND STRENGTHS
Extended-release injection: 10 mg/0.4 mL in a single-dose, pre-filled syringe.

CONTRAINDICATIONS
SUSTOL is contraindicated in patients with hypersensitivity to granisetron, any of the components of SUSTOL, or to any of the other 5-HT3 receptor antagonists.

WARNINGS AND PRECAUTIONS
Injection Site Reactions (ISRs), Including Infection, Bleeding, Pain, Nodules, Swelling, and Induration: Monitor patients for ISRs following SUSTOL injection. Inform patients that some ISRs may occur 2 weeks or more after SUSTOL administration. In patients receiving antiplatelet agents or anticoagulants, consider the increased risk of bruising or severe hematoma prior to the use of SUSTOL. In patients with ongoing or unresolved ISRs, administer SUSTOL at a site away from areas affected by ISRs.

Gastrointestinal Disorders: Monitor for constipation and, when applicable, consider optimizing patients' current bowel regimens for managing preexisting constipation. Also monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. Instruct patients to seek immediate medical care if signs and symptoms of ileus occur. In clinical trials, 224 of 1131 (20%) of patients treated with SUSTOL 10 mg reported constipation compared to 13% to 15% in the 5-HT3 receptor antagonist control arms. Hospitalization due to constipation or fecal impaction was reported in 5 SUSTOL-treated patients (0.3%).

Hypersensitivity Reactions: Serious reactions have been reported and may occur up to 7 days or more after SUSTOL administration and may have an extended course. If a reaction occurs, administer appropriate treatment and monitor until signs and symptoms resolve.

Serotonin Syndrome: Serotonin syndrome has been reported with 5-HT receptor antagonists alone, but particularly with concomitant use of serotonergic drugs (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.
Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of SUSTOL and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue SUSTOL and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if SUSTOL is used concomitantly with other serotonergic drugs.

ADVERSE REACTIONS
Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of a 10 mg subcutaneous dose of SUSTOL was evaluated in two double-blind, randomized, active-controlled studies, in which 210 patients (23%) received MEC and 467 patients (51%) received AC combination chemotherapy. The data described below reflect exposure to a single 10 mg dose of SUSTOL in 924 patients whose mean age was 56 years (range 19 to 91 years); 76% of patients were female; 70% of patients were Caucasian, 16% Asian, 10% Black, and 4% other races. Dexamethasone was co-administered with SUSTOL in Study 1 and Study 2 and an NK1 receptor antagonist was co-administered with SUSTOL in Study 2.
Table 1 lists the most common adverse reactions reported in at least 3% of patients following a single dose of SUSTOL 10 mg in Study 1 and/or Study 2. Overall, ISRs were the most common group of adverse reactions in SUSTOL-treated patients. Specific types of ISRs reported by SUSTOL-treated patients are shown in Table 2.

Table 1. Adverse Reactions Occurring in at Least 3% of Patients Treated with SUSTOL 10 mg in Study 1 and/or Study 2

	Study 1		Study 2	
Adverse Reaction	**SUSTOL 10 mg subcutaneous (N=468) %**	**Palonosetron hydrochloride 0.25 mg intravenous (N=463) %**	**SUSTOL 10 mg subcutaneous (N=456) %**	**Ondansetron 0.15 mg/kg intravenous (N=459) %**
Injection Site Reactions, any[a]	37	15[b]	62	See footnote[b]
Constipation	14	11	22	15
Fatigue	11	10	21	24
Headache	9	9	13	19
Diarrhea	8	7	9	8
Abdominal Pain	7	7	7	4
Insomnia	4	2	5	6
Dyspepsia	3	3	6	7
Dizziness	3	2	5	5
Asthenia	4	6	2	2
Gastroesophageal Reflux	1	1	5	4

[a] Rates of individual injection site reactions (ISRs) are shown in Table 2.
[b] The placebo subcutaneous injection for Study 1 was normal saline and for Study 2 was a SUSTOL-matched control consisting of the SUSTOL polymer vehicle without active drug.

Table 2. Injection Site Adverse Reactions Following a Single 10 mg SUSTOL Dose

Injection Site Reaction	Study 1 Treatment Arm (Subcutaneous Injection)		Study 2[a,b] SUSTOL (N=456) %
	SUSTOL (N=468) %	Saline Control (N=463) %	
Total Subjects with at least 1 ISR	37	15	62
Pain	3	1	20
Tenderness	4	1	27
Bruising/Hematoma	22	10	45
Bleeding	2	1	4
Erythema/Redness	11	3	17
Swelling/Induration	1	0	10
Mass/Nodule	11	1	18
Infection at injection site	<1	0	1
Other[c]	2	1	1

[a] Patient diary was used in Study 2 to collect ISR information daily.
[b] The placebo subcutaneous injection for Study 2 was a SUSTOL-matched control consisting of the SUSTOL polymer vehicle without active drug. ISR data for this group are not shown.
[c] Other includes injection site discoloration, vesicles, irritation, lipoma, paresthesia, pruritus, rash, reaction, scab, scar, and warmth.

ISRs occurred in 37% (175/468) in Study 1, Cycle 1 only, and 62% (281/456) in Study 2 of SUSTOL-treated patients. The ISR manifestations included pain, erythema, mass/nodule, swelling/induration, and bleeding. The incidence of individual ISRs is shown in Table 2. Patients may have experienced one or more types of ISRs; a total of 213 of 924 patients had three or more. ISR reporting procedures included both investigator- and patient-reported outcomes in Study 2, while Study 1 used only investigator reporting.

DRUG INTERACTIONS
Serotonergic Drugs: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including SSRIs and SNRIs. Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue SUSTOL and initiate supportive treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary: There are no available data on the use of SUSTOL in pregnant women. Limited published data on granisetron use during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits administered granisetron hydrochloride during organogenesis at intravenous doses up to 61 times and 41 times, respectively, the maximum recommended human dose (MRHD) of SUSTOL 10 mg/week [see Animal Data].
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Animal Data: Reproduction studies with granisetron hydrochloride have been performed in pregnant rats following administration during the period of organogenesis at intravenous doses up to 9 mg/kg/day (approximately 61 times the MRHD of SUSTOL 10 mg/week, based on body surface area) and oral doses up to 125 mg/kg/day (approximately 851 times the MRHD of SUSTOL 10 mg/week, based on body surface area). Reproduction studies have been performed in pregnant rabbits in which granisetron hydrochloride was administered during the period of organogenesis at intravenous doses up to 3 mg/kg/day (approximately 41 times the MRHD of SUSTOL 10 mg/week, based on body surface area) and at oral doses up to 32 mg/kg/day (approximately 436 times the MRHD of SUSTOL 10 mg/week, based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to granisetron hydrochloride.
Reproduction studies with the polymer vehicle for SUSTOL have been performed in pregnant rats and rabbits following administration of the polymer vehicle during the period of organogenesis at subcutaneous doses up to 0.295 g and 1.18 g per day, respectively (approximately 45 and 36 times, respectively, the amount of polymer vehicle present in the maximum recommended/weekly single human dose of SUSTOL, based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to the polymer vehicle. A pre- and postnatal development study with the polymer vehicle for SUSTOL in rats showed no evidence of any adverse effects on pre- and postnatal development at subcutaneous doses (administered on gestation days 7 through lactation day 20) up to 0.295 g per day (approximately 45 times the amount of polymer vehicle present in the maximum recommended/weekly single human dose of SUSTOL, based on body surface area).

Lactation: There are no data on the presence of SUSTOL in human milk, the effects of SUSTOL on the breastfed infant, or the effects of SUSTOL on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of SUSTOL to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUSTOL and any potential adverse effect on the breastfed infant from SUSTOL or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of SUSTOL in pediatric patients under 18 years of age have not been established.

Geriatric Use: Of the 738 patients administered 10 mg of SUSTOL in the comparator-controlled studies, 177 (24%) were 65 and over while 39 (5%) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment: Breakdown products of the polymer vehicle in SUSTOL can be detected in urine of healthy subjects. There are no pharmacokinetic data regarding elimination of the polymer vehicle of SUSTOL in patients with renal impairment and the clinical significance of potential prolonged elimination is not known. Avoid SUSTOL in patients with severe renal impairment. In patients with moderate renal impairment, do not administer SUSTOL more frequently than once every 14 days.

OVERDOSAGE
There is no specific antidote for granisetron overdosage. In the case of overdosage, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride, as a single intravenous injection, has been reported without symptoms or with only the occurrence of headache.

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was defined from initiation of the LOT to initiation of subsequent LOT; Kaplan-Meier analysis determined the duration of treatment (DOT) and TTNT. Treatment regimens were classified into the following 6 mutually-exclusive categories:

- Bortezomib (bor)
- Lenalidomide (len)
- Pomalidomide (pom)
- Carfilzomib (car)
- Thalidomide (thal)
- Other therapies

For the eligible patient population, the healthcare resource utilization and the monthly cost for each patient were calculated. The total costs included inpatient, outpatient, and pharmacy costs.

During a 20-month follow-up period among the 9960 patients (57.4% of whom were male) following the first line of therapy, 3282 (33.0%), 1103 (11.1%), and 400 (4%) patients initiated second-, third-, and fourth-line treatment, respectively. The most common third-line treatment included bor-based (43.5%, including 10.5% for bor-len) and len-based regimens (29.8%), the authors report.

BORTEZOMIB- AND/OR LENALIDOMIDE-BASED REGIMENS REMAINED THE MOST COMMONLY USED THERAPIES IN THE THIRD-LINE SETTING FOR RELAPSED/ REFRACTORY MULTIPLE MYELOMA, DESPITE THE AVAILAIBILITY OF NEW TREATMENTS.

Median DOTs ranged from 3.7 months for car-based regimens to 8.1 months for len-based regimens; median TTNT was car-, pom-, bor-, len-, other-, and thal-based regimens—in increasing order. Each patient with rrMM averaged 4.5 outpatient visits, 0.1 inpatients visits, 0.1 emergency department visits, and 0.004 hospice care visits each month. The authors estimated the following average monthly costs for each patient:

- Bor-based regimens: $14,286
  - » Bor monotherapy: $10,838
  - » Bor-len: $17,917
  - » Bor-other: $16,359
- Len-based regimens: $13,377
  - » Len monotherapy: $11,859
  - » Len-other: $23,746
- Pom-based regimens: $25,850
  - » Pom monotherapy: $20,121
  - » Pom-other: $44,402
- Car-based regimens: $21,180
  - » Car monotherapy: $20,322
  - » Car-other: $24,283
- Thal-based regimens: $11,919
  - » Thal monotherapy: $12,066

The retrospective analysis showed that bor- and/or len-based regimens remained the most commonly used therapies in the third-line setting despite the addition of new treatments to the armamentarium of available options. Further, the monthly treatment costs per patient were higher for pom- and car-based regimens, the authors report. ◆

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Shao C, Monberg M, Cao X, Zhou W, Zhong Y, Marinello P. Real-world treatment patterns, health care utilization, and costs among relapsed/ refractory multiple myeloma (rrMM) patients. Presented at: 58th American Society of Hematology Annual Meeting & Exposition; December 4, 2016; San Diego, CA. Abstract 3555.

Innovative Approach to Precision Trial Design: NCI MATCH and Beat AML

Surabhi Dangi-Garimella, PhD

DRUKER

FLAHERTY

Brian Druker, MD, is director of the Knight Cancer Institute, Oregon Health & Science University.

Keith Flaherty, MD, is director of the Henri and Belinda Termeer Center for Targeted Therapies at Massachusetts General Hospital; associate professor of Medicine, Harvard Medical Center.

WHILE ON THE ONE HAND, researchers and drug developers are identifying molecular targets in specific cancer subtypes to improve outcomes, they have also been innovating on the clinical trial design front. At a late session during the 58th American Society of Hematology Annual Meeting & Exposition, held December 3-6 in San Diego, CA, representatives from 2 national clinical trials, Beat AML (acute myeloid leukemia) and NCI-MATCH (National Cancer Institute-Molecular Analysis for Therapy Choice), detailed how they were incorporating genomic profiling to assign patients to different treatment arms.

Providing an update on the Beat AML trial was Brian Druker, MD, director of the Knight Cancer Institute at Oregon Health & Science University, which is collaborating with the Leukemia & Lymphoma Society on the trial. Providing a background on the disease, Druker said that AML is the most common leukemia in adults, with a median age at diagnosis of 67 years, and although the dozens of different molecular subtypes make it a very complicated disease to treat, a few targeted agents have seen some progress in treating AML, including spleen tyrosine kinase inhibitors, IDH1/2 agents, kinases (FLT3, KIT), and the more recent immune checkpoint inhibitors.

However, despite all the progress with characterizing the molecular abnormalities associated with the disease, progress on the treatment front has been dismal. "Treatment evolution for AML has lacked significantly," Druker said, adding that disease outcomes have remained poor over the past decade and there have been very few approvals. "The fact that AML is a very heterogeneous disease could also have a role to play," he added.

In addition, conducting a clinical trial for AML remains a hurdle, Druker noted. "Challenges include the fact that the standard of care remains beneficial, single-agent treatment will not be beneficial, genomic assays take long to deliver, and trials are hard to recruit for." With all these challenges, the Beat AML trial has been designed with the following objectives:

1. Perform genomic screening of patients at clinical trial entry
2. Assess the feasibility of waiting 7 days for the genomic test results
3. Assign therapy based on genomic screening
4. Incorporate a marker-negative arm so all patients have a treatment option
5. Provide a network for junior clinical investigators

The trial has a multi-arm protocol, with:

1. Each arm independent from the other, with consistent eligibility
2. Window design ensuring documentation of all large effects in treatment-naïve patients
3. Initial focus on those 60 and older

Trial eligibility criteria are straightforward: patients 60 years and older who have previously untreated AML can participate. Following genomic analysis of their tissue, patients will be assigned to independent treatment arms in the protocol.

"The primary objective of the Beat AML trial is to assess the feasibility of trial design," Druker said. "Secondary objectives are to determine how many patients can be successfully enrolled, determine if patients can reach allogenic stem cell transplant, and assess impact on outcomes." He listed the treatment substudies and their start date, as shown in the **TABLE**.

TABLE. Treatment Substudies in the Beat AML Trial

AML SUBTYPE	DRUG	START DATE
Tet2/WT1/IDH1	CD33 (BI 836858) + Aza	November 2016
CBF	CD200 (Samalizumab) + induction	November 2016
Marker negative	CD33 (BI 836858) + Aza	November 2016
MLL/MLL-PTD	SYK inhibitor (Entospletinib)	December 2016
IDH2	IDH 2 inhibitor (AG221) +/- Aza	December 2016
NPM1	In negotiations	February 2017
p53/complex karyotype	In negotiations	February 2017
FLT3	FLT3 inhibitor + decitabine	April 2017
IDH1 mutation	IDH 1 inhibitor	April 2017

ACRONYM	STANDS FOR
AML	Acute myeloid leukemia
CBF	Core binding factor
IDH1/2	Isocitrate dehydrogenase 1/2
FLT3	FMS-like tyrosine kinase 3
MLL	Mixed-lineage leukemia
MLL-PTD	Mixed-lineage leukemia protein transduction domains
SYK	Spleen tyrosine kinase
Tet2	Tet methylcytosine dioxygenase 2
WM1	Wilms tumor 1

For biomarker assessment, Druker said that cytogenetics assays will be local. Meanwhile, biopsy samples will be sent to Foundation Medicine to conduct a more long-term 300-gene panel assay. "However, critical genes will be assayed by the company in 7 days, including *NPM1, IDH1/2, and FLT3*."

The order of patient assignment to a treatment arm will be based on:

1. Chemotherapy response
2. Molecular marker with high variant allele frequency
3. Higher-risk group that may confound efficacy
4. Marker negative

Trial endpoints are standard, Druker told the audience, and include primary endpoints of complete response and response duration. Secondary endpoints include event-free survival, progression-free survival (PFS), overall survival, and minimal residual disease.

Still in its early stages of conception, Beat AML has "enrolled 4 patients to date," Druker said. "The goal is to allow patients to be enrolled in active treatment arms, and the master protocol allows switching between the arms." He added that in the future, the trial would like to include additional arms on the protocol and test novel combinations.

The second presentation of the session, by Keith Flaherty, MD, provided an update on the NCI-MATCH trial. Flaherty, director of the Henri and Belinda Termeer Center for Targeted Therapies at Massachusetts General Hospital and associate professor of medicine at Harvard Medical Center, also chairs ECOG-ACRIN, which is collaborating with NCI on this trial. He was very excited to share with the audience that the trial was expected to hit it's 6000 patient enrollment target in the next 6 months.

"We are currently enrolling 120 to 150 patients being each week," Flaherty said. "The objective of this phase 2 precision-med trial is to match genetic abnormalities of tumors with a suitable targeted drug, regardless of cancer type," he explained. "It's a signal-finding trial, meaning promising treatments can be expanded to a more definitive trial in the future."

Eligibility criteria for enrollment in NCI-MATCH include adults over 18 years, those who lack or have exhausted standard treatment, patients who have developed either solid or liquid tumors, patients with a good ECOG performance status and adequate organ function, and patients who can tolerate being off treatment for 6 weeks. Flaherty listed the following criteria for source material for genetic and immunohistochemistry analysis:

1. The trial mandates a fresh tumor biopsy to identify gene abnormalities
2. Patients can be screened with local next-generation sequencing, but results have to be confirmed on an NCI-MATCH assay
3. Biopsy and sequencing on progression for responders
4. Planned assays for research purposes:
   a. Whole-exome DNA sequencing
   b. RNA analysis by whole transcriptome analysis
   c. microRNA assay

The following Levels-of-Evidence strategy is being implemented by NCI-MATCH:
Level 1: gene variant credentialed for selection of an approved drug
Level 2a: variant eligible for an ongoing clinical trial
Level 2b: variant identified in an N of 1 response
Level 3: preclinical inferential data

Levels of Evidence for drugs in NCI-MATCH include:
Level 1: FDA-approved for any indication for that target
Level 2: agent met a clinical endpoint, with evidence of target inhibition
Level 3: agent demonstrated evidence of clinical activity, with evidence of target inhibition at some level

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Among the 6000 patients that will be the final enrollment, 929 treatment enrollments are anticipated across 24 gene abnormalities that are currently being evaluated as part of this trial. The primary trial endpoint is overall response rate, with secondary endpoints of PFS, time to progression, toxicity, and biomarker expression.

Flaherty explained that the trial demands 4 core biopsies at initial entry, which are shipped to the central lab at MD Anderson. H&E sections are assayed by a pathologist for tumor type, content, percent necrosis, and inflammation, and scanned into a high-resolution image database. RNA and DNA are then extracted and distributed to a network of laboratories.

"[NCI-MATCH] IS A SIGNAL-FINDING TRIAL, MEANING PROMISING TREATMENTS CAN BE EXPANDED TO A MORE DEFINITIVE TRIAL IN THE FUTURE."

-KEITH FLAHERTY, MD

Currently, immunohistochemistry analysis is being conducted for PTEN, MLH1, MSH2, and Rb. "We have also added mismatch repair genes and are evaluating PD-1 expression," he added. The trial has incorporated a customized Oncomine assay, which has been developed by Thermo Fisher. The panel includes 143 genes, 2530 amplicons in the DNA panel, and 207 amplicons in the RNA panel. Flaherty provided a very uplifting picture on patient wait times:

- Sample submission from sites to central lab at MD Anderson: 7 days
- Completion of tumor testing by lab network and return of results to site: 15 days
- Secondary screening for patients assigned to a treatment arm: 14 days.

"As of November 27, we have 3149 patients with tumor samples, of whom 2589 have received their test results; 468 had a genetic abnormality matching an available treatment," Flaherty told the audience, "and 22% of currently enrolled patients have a gene abnormality that matches one being studied in the trial." Although the trial currently has 24 arms, this number is expected to increase. ◆

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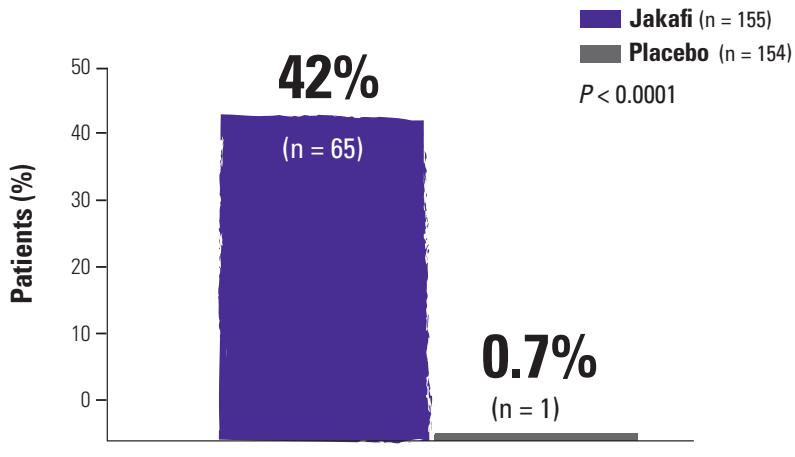
In COMFORT-I* and COMFORT-II,† Jakafi® (ruxolitinib) significantly reduced spleen volume compared with patients receiving placebo or best available therapy, respectively[1-3‡]

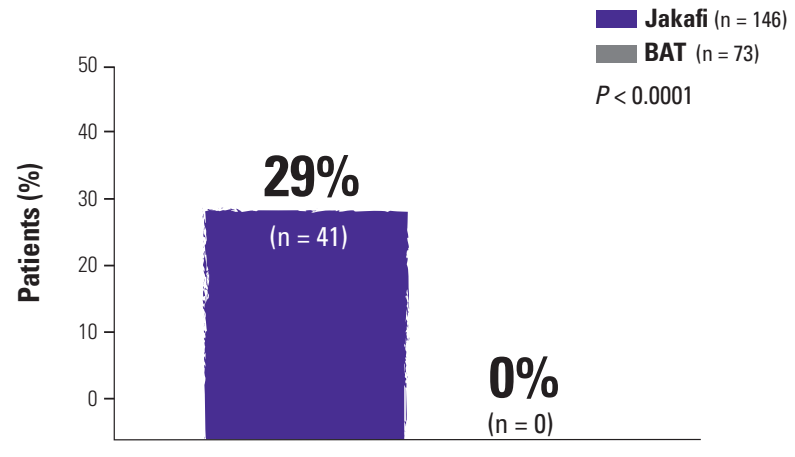
- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 24 as measured by CT or MRI[1,2]

COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24[1,2]



- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI[1,3]

COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48[1,3]



BAT, best available therapy.

* COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk or high-risk myelofibrosis.[1,2]

† COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk or high-risk myelofibrosis.[1,3]

‡ Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[4]

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Incyte

Jakafi® ruxolitinib (tablets)

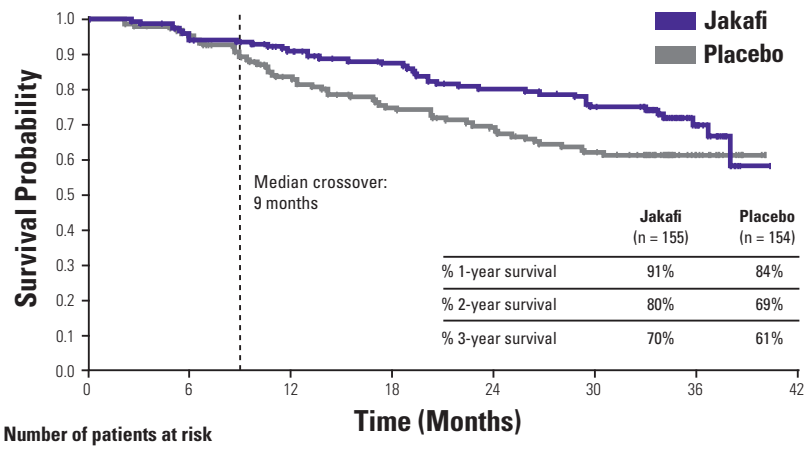
Indications and Usage

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II[1]

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to best available therapy[1]

COMFORT-I Overall Survival: Kaplan-Meier Curves by Treatment Group[1]

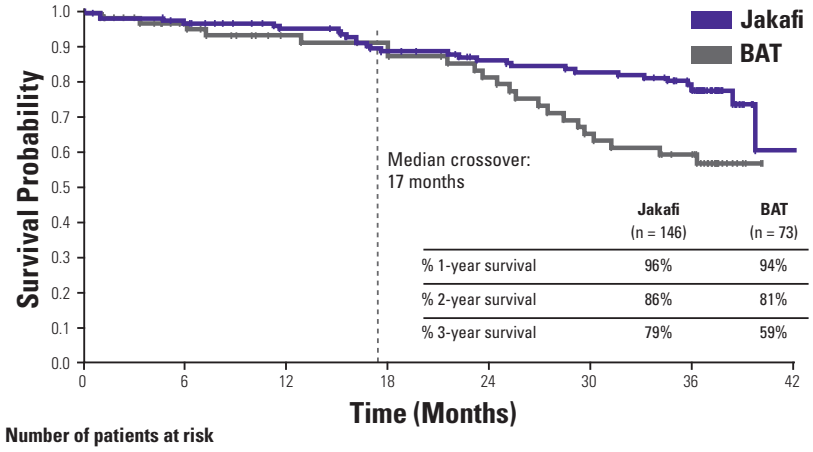


	Jakafi (n = 155)	Placebo (n = 154)
% 1-year survival	91%	84%
% 2-year survival	80%	69%
% 3-year survival	70%	61%

Number of patients at risk

Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

COMFORT-II Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



	Jakafi (n = 146)	BAT (n = 73)
% 1-year survival	96%	94%
% 2-year survival	86%	81%
% 3-year survival	79%	59%

Number of patients at risk

Jakafi	146	135	126	115	107	104	33	0
BAT	73	58	50	47	42	33	9	0

BAT, best available therapy.

- Because of progression-driven events or at the physician's discretion, patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes[4]
- All patients in the placebo group either crossed over or discontinued[1]

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit **Jakafi.com/HCP**.

References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807. **3.** Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798. **4.** Data on file. Incyte Corporation. Wilmington, DE.

Jakafi®
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *PML* Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience in Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions **Anemia** In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. **CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Fluconazole:** The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole at doses of 100 mg to 400 mg once daily, respectively [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Pharmacokinetics (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: *Risk Summary* There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of patients with myelofibrosis in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [*see Dosage and Administration (2.4) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

Revised: March 2016 RUX-1778a

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PROGRAM OVERVIEW

- Nominations are open through March 20, 2017.
- Domestic and international nominations will be accepted. Self-nominations are permitted and encouraged.
- The *Giants of Cancer Care*® Advisory Board will vett all nominations to determine finalists in each category.
- A Selection Committee of 90+ oncologists will vote to determine the 2017 winners.
- The 2017 *Giants of Cancer Care*® class of inductees will be announced in Chicago on June 1, 2017.

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