Bridging the gap between payer and provider perspectives

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Evidence-Based Oncology™

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Highlights from the 56th ASH Annual Meeting & Exposition

AMERICAN SOCIETY OF HEMATOLOGY

Highlights Include:

- Experts Seek Solutions to the Rising Costs of Therapy
- Therapeutic Options for Chronic Myelogenous Leukemia
- New Role for the FDA in Regulating Molecular Diagnostics
- TKIs and Molecular Response in CML
- Early Treatment and Monoclonal Antibodies in Multiple Myeloma
- Strong Response to Ibrutinib Combination in Hard-to-Treat MCL

imbruvica®
(ibrutinib) 140mg capsules

NEW PHASE 3 DATA

IMBRUVICA® demonstrated single-agent survival in previously treated CLL

INDICATIONS: IMBRUVICA® is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of patients with:

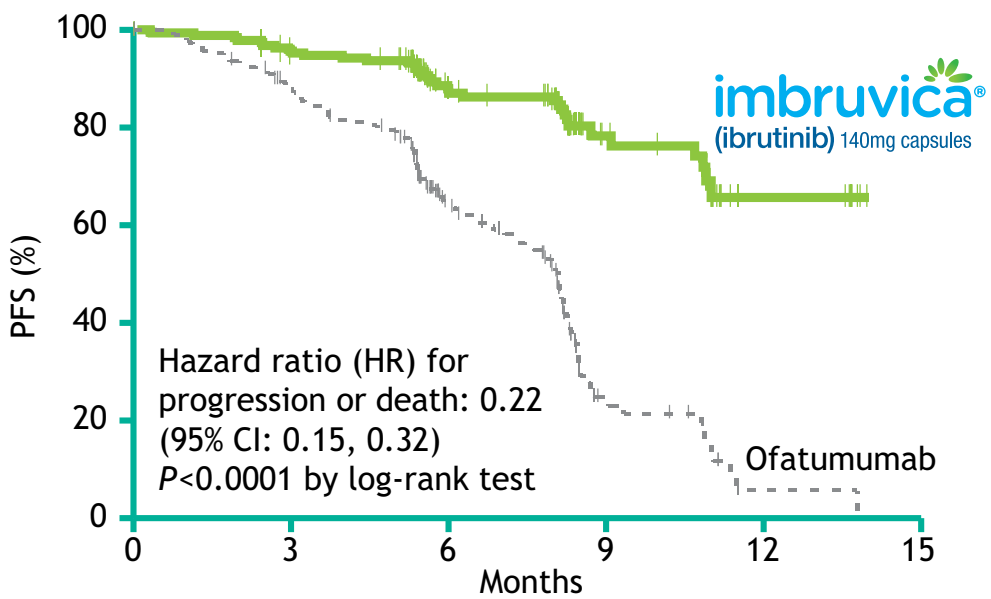
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- CLL with 17p deletion

Significantly improved overall survival (OS)—secondary endpoint

- 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA® arm (HR=0.43; 95% CI: 0.24, 0.79)
- Median OS not yet reached in either treatment arm
- 29% of ofatumumab patients crossed over to receive IMBRUVICA® upon progression

Significantly extended progression-free survival (PFS)—primary endpoint

78% statistically significant reduction in the risk of death or progression (independent review)



Number at risk

IMBRUVICA®	195	183	116	38	7	0
Ofatumumab	196	161	83	15	1	0

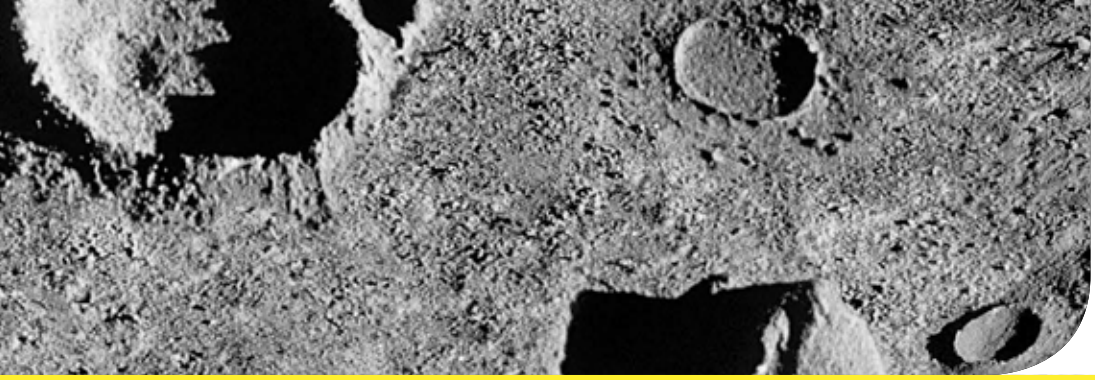
Results from the randomized, multicenter, open-label, Phase 3 RESONATE™ trial of IMBRUVICA® vs ofatumumab in patients with previously treated CLL. Patients (N=391) were randomized 1:1 to receive either IMBRUVICA® 420 mg orally daily until disease progression or unacceptable toxicity or IV ofatumumab at an initial dose of 300 mg, followed 1 week later by a dose of 2000 mg weekly for 7 doses, and then every 4 weeks for 4 additional doses. Fifty-seven patients randomized to ofatumumab crossed over following Independent Review Committee-confirmed progression to receive IMBRUVICA®. Primary endpoint: PFS as assessed by an Independent Review Committee (IRC) according to modified International Workshop on CLL Criteria.

Significantly improved PFS in patients with previously treated del 17p CLL

- 75% reduced risk of progression or death (HR=0.25; 95% CI: 0.14, 0.45)
  - Median PFS not reached with IMBRUVICA® vs 5.8 months with ofatumumab

In CLL studies, approximately 5% of patients discontinued due to adverse events

Please review the Important Safety Information on adjacent page.



imbruvica®
(ibrutinib) 140mg capsules

ORAL, ONCE-DAILY DOSING

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Grade 3 or higher bleeding events (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 anti-platelet or anti-coagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA®. Twenty-six percent of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with 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, 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. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

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®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in the clinical trials were thrombocytopenia (56%), neutropenia (51%), diarrhea (51%), anemia (37%), fatigue (28%), musculoskeletal pain (28%), upper respiratory tract infection (28%), rash (26%), nausea (25%), and pyrexia (24%). Approximately 5% of patients receiving IMBRUVICA® discontinued treatment due to adverse events. These included infections, subdural hematomas, and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid concomitant administration with strong or moderate inhibitors of CYP3A. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with baseline hepatic impairment.

Please review the Brief Summary of full Prescribing Information on the following page.

To learn more, visit us at
www.IMBRUVICA.com

07/14 PRC-00483

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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. Improvements in survival or disease-related symptoms have not been established. 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: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2) in full Prescribing Information].*

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Grade 3 or higher bleeding events (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.

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. Twenty-five percent of patients with MCL and 26% of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) *[See Adverse Reactions].* Monitor patients for fever and infections and evaluate promptly.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 23 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with 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, 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. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification *[see Dosage and Administration (2.3) in full Prescribing Information].*

Second Primary Malignancies: Other malignancies (range, 5 to 10%) including carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 8%).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. 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]*
- Second Primary Malignancies *[see Warnings and Precautions]*

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)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative 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: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included

48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
Infections and infestations	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

**One patient death due to histiocytic sarcoma.*

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

IMBRUVICA® (ibrutinib) capsules

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.

Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2

System Organ Class ADR Term	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				
Fatigue	28	2	30	2
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

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors: 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: Pregnancy Category D *[see Warnings and Precautions].*

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. 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.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral 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 post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL 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 animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Nursing Mothers: It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether 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 IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2) in full Prescribing Information].*

IMBRUVICA® (ibrutinib) capsules

Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

Hepatic Impairment: Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical trials. There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

Females and Males of Reproductive Potential: Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations].*

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (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) 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].*
- *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].*
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[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 (2.5) 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, Inc.
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

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

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PUBLISHER'S NOTE

SP6 Novel Treatments, Value of Care, and Healthcare Costs Discussed at the 56th Annual ASH Meeting

QUALITY & VALUE

SP7 Healthcare Costs in Need of Solutions: Experts at ASH Agree
SURABHI DANGI-GARIMELLA, PhD

SP8 Care Plans to Reduce Healthcare Utilization in Sickle Cell Disease
SURABHI DANGI-GARIMELLA, PhD

SP9 Session on Survivorship Outlines Surveillance Strategies in Non-Hodgkin Lymphoma
MARY K. CAFFREY

SP10 ASH Presents Second Round of Tests, Treatments to Question Under *Choosing Wisely* Initiative
MARY K. CAFFREY

MULTIPLE MYELOMA

SP12 Early Treatment, Monoclonal Antibodies Discussed in Multiple Myeloma
MARY K. CAFFREY

SP12 Promising Results for Elotuzumab Presented in Session on Multiple Myeloma
MARY K. CAFFREY

SP13 Sessions Report Phase 2 Results of Pomalidomide Combinations
MARY K. CAFFREY

CHRONIC MYELOGENOUS LEUKEMIA

SP14 CML Updates: Defining MMR and Results of the DASISION Trial
SURABHI DANGI-GARIMELLA, PhD

SP17 Poster Presentations Cover Therapeutic Options in CML
SURABHI DANGI-GARIMELLA, PhD

SP18 SPIRIT 2: Dasatinib Superior to Imatinib in Newly Diagnosed CML
SURABHI DANGI-GARIMELLA, PhD

RESEARCH REPORT

SP18 Ibrutinib Demonstrates Significant Responses for Patients With Hard-to-Treat CLL/SLL, Phase 2 Data Show
MARY K. CAFFREY

SP24 Results Project Savings for Payers With Novel Oral Anticoagulants
MARY K. CAFFREY

SP24 Study Suggests Method of Reducing Blood Clots Without Risking Bleeding
MARY K. CAFFREY

SP25 Best of ASH Presentations: Platelets, Lenalidomide for MDS, and Sorafenib in AML
SURABHI DANGI-GARIMELLA, PhD

SP26 Data Show High Response Rate to Ibrutinib Combination for Patients With Hard-to-Treat MCL
SURABHI DANGI-GARIMELLA, PhD

ONCOLOGY STAKEHOLDER SUMMIT

SP27 Improved Cancer Care Through Innovation
SURABHI DANGI-GARIMELLA, PhD

SP30 Payers Look to CER for Improved Healthcare Decisions
SURABHI DANGI-GARIMELLA, PhD

FDA UPDATE

SP32 Bigger Regulatory Challenges in Diagnostics Than in Therapeutics, Industry Expert Says
MARY K. CAFFREY

Results presented at the 56th Annual Meeting of ASH from a phase 2 trial let by MICHAEL WANG, MD, *(left) of the MD Anderson Cancer Center in Houston, showed that 88% of patients with relapsed or refractory mantle cell lymphoma responded to a combination of ibrutinib and rituximab.*

Novel Treatments, Value of Care, and Healthcare Costs Discussed at the 56th Annual ASH Meeting

The annual meeting of the American Society of Hematology (ASH), perennially the largest global gathering of hematology scientists and clinicians, provides an excellent platform for experts in the field to share, discuss, and collectively shape the future direction of research.

The 56th annual meeting, held December 6-9, 2014, at the Moscone Center in San Francisco, did not disappoint. Added this year was a session on new FDA-approved therapies in hematology, which addressed issues important for clinicians to understand when prescribing a novel drug. Another highlight was a quality symposium exploring the increasing cost of care and its impact on the lives of patients and their families. As chronicled in this issue, the session spawned a heated discussion among clinicians, patients, patient representatives, and members of the pharmaceutical industry as they attempted to identify a way out of the unsustainable healthcare expenditure which totaled $3.8 trillion in the United States in 2013.

To address quality, ASH announced its latest recommendations under the *Choosing Wisely* initiative, advising physicians on the appropriate use of anticoagulants, when to transfuse sickle cell patients, and surveillance scans in patients with chronic lymphocytic leukemia. A separate education session complemented one of the *Choosing Wisely* recommendations: Christopher R. Flowers, MD, MS, presented data that drew attention to the high costs of unnecessary imaging, such as computed tomography and positron emission tomography, to detect relapse in lymphoma patients. While highlighting the importance of follow-up imaging, Flowers concluded, "Good clinical judgment remains the cornerstone of patient care."

Among other highlights of the meeting we have covered for you are promising results in chronic myelogenous leukemia, multiple myeloma, and anticoagulant therapy.

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Sincerely,

Brian Haug
President, *The American Journal of Managed Care*

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.

Healthcare Costs in Need of Solutions: Experts at ASH Agree

Surabhi-Dangi Garimella, PhD

As medical oncologists, drug developers, and research scientists presented findings and novel treatment options in hematological cancers, a special session on the first day of the 56th Annual Meeting of the American Society of Hematology (ASH), held December 6-9, 2014, in San Francisco, addressed an aspect of cancer care that's increasingly finding its way onto the agenda at clinical meetings, as was witnessed at the annual meeting of the American Society of Clinical Oncology (ASCO).[1]

The session, "The Rising Cost of Medical Care: Understanding the Problem and Exploring Solutions," drew participation from hematologists and a representative from a company that provides market access support to the pharmaceutical industry. These experts came together on a common platform to discuss ways to tame the unsustainable healthcare expenditure in the United States, which touched $3.8 trillion in 2013.[2]

Escalating drug costs can influence patient adherence, quality of life, and overall health—an endless loop. Participants in this energetic discussion provided insight into these existing challenges and ways to address them.

Hagop M. Kantarjian, MD

Kicking off the session was Hagop M. Kantarjian, MD, professor, Department of Leukemia, the University of Texas MD Anderson Cancer Center in Houston, Texas. Kantarjian presented strong views on the way the pharmaceutical industry sets drug prices during his talk, "Cancer Drug Prices in the US: Causes, Consequences and Solutions." He said he is surprised by the high drug prices today, the triggers for him being the prices for 3 commonly used drugs for chronic myelogenous leukemia (CML): ponabinostat, bosutinib, and omacetaxine. Each of the 3 drugs costs more than $100,000 per year. While cancer drug prices have been rapidly rising—a 10-fold increase over the past decade—the average household income, he said, has decreased by 8%. Kantarjian asked the audience to come up with solutions to help these patients who might be victimized in the process. High out-of-pocket costs, he said, are leading patients to personal bankruptcy, adherence issues, and mental stress; results show that 10% of patients abandon treatment and 20% have poor compliance.

Kantarjian came down hard on the pharmaceutical industry for overestimating the amount spent on developing a drug. "The billion-dollar price tag per drug does not account for the 50% tax subsidy that they avail, and it's the mean cost, not median," he said. Kantarjian concluded his talk by providing several solutions to this growing problem:

- increased/continued participation by organizations like ASCO and ASH in the discussion
- allowing Medicare to negotiate the price of drugs they buy from the pharmaceutical manufacturers
- allowing importing of drugs
- preventing "pay-for-delay," which blocks all other generic drug competition for a growing number of branded drugs.

Providing a nearly opposite opinion was Alex W. Bastian, MBA, vice president, market access, GfK Bridgehead. During his talk, "Hematology Drug Pricing in America: Moving to a Sustainable Model," Bastian acknowledged that while the unsustainable drug costs cannot be ignored, the healthcare community must focus its attention on value of therapy rather than cost, which echoed the ASCO initiative. Bastian went on to emphasize, however, that the Uni ted States is not alone in this problem; rising healthcare costs are a global phenomenon.

He presented the real-world situation: with the success of innovation and research, dramatic survival gains have been achieved in hematology over the past half century. However, an examination of the statistics reveals that while FDA-approved drugs have steadily increased between 1998 and 2014, 249 hematology drugs have failed during the same period. These failures, according to Bastian, need to be accounted for.

He reiterated the importance of identifying the value of therapy. "We need a long-term view of the situation, taking into consideration the total benefits that a drug might yield," which can reduce the downstream cost of care.

S. Yousuf Zafar, MD, MHS, associate professor of medicine at Duke University, was the next member of the panel to share his thoughts. Zafar, a medical oncologist by training, is a health service researcher with an interest in improving care delivery for advanced cancer patients. His research focus includes studying the impact of cost of cancer care on patient preferences with cost-related communication and decision making.[3]

During his presentation, Zafar alluded to the substantial financial burden of the high cost of care on cancer patients and survivors, which can impair their quality of life and diminish the quality of their care. He said that coupled with chemotherapy side effects, cancer treatment can be financially toxic. A study from Fred Hutchison Cancer Center published last year reported that people diagnosed with cancer are more than 2.5 times more likely to declare bankruptcy than those without cancer.[4] Zafar alluded to the fact that financial toxicity can also impact quality of care, as it puts patients at risk for cost-related nonadherence with their anticancer therapy; studies have demonstrated decreased adherence to tyrosine kinase inhibitors in patients with chronic myeloid leukemia, he said.

Zafar used a case study of a patient in his clinic. He made a case that his patient lacked prescription drug benefits through his employer, which resulted in him refusing advanced therapy when his cancer metastasized. The patient told Zafar that he simply could not afford to pay for the treatment. Using this paradigm, Zafar suggested that physicians, patients, and policy makers face a growing mandate to integrate costs into clinical decision making.

However, little is known about patients' preferences for incorporating cost discussions into cancer treatment decision making or about the ramifications of those discussions. Zafar's research group conducted a prospective longitudinal study to determine if patients wanted to discuss the costs of treatment with doctors, if patients wanted to incorporate costs into treatment decision making, and if patients found cost discussions useful in lowering out-of-pocket expenses. Of 300 patients surveyed (86% response rate), 52% expressed some desire to discuss treatment-related out-of-pocket costs with their doctor, and 51% wanted their doctor to take costs into account to some degree when making treatment decisions. Only 19% had talked to their doctor about their cost of care, and of those, 57% reported lower out-of-pocket costs following the discussions. While cancer patients varied in their desire to discuss costs with doctors, those who did follow through on the discussion believed that the conversations helped reduce their expenses.

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"Our study highlights that patient-physician cost communication can reduce out-of-pocket costs even in oncology, where treatment options are often limited," he said. While heterogeneity was observed among patients with respect to preferences on cost discussion, a significant number of those who broached the topic found help in reducing their expenses despite well-described barriers to effective cost discussions, Zafar concluded. **EBO**

References

1. The oncologist defines value of care. *Am J Manag Care.* 2014;20(12):SP359-SP360.

2. Munro D. Annual US healthcare spending hits $3.8 trillion. Forbes website. http://www.forbes.com/sites/danmunro/2014/02/02/annual-u-s-healthcare-spending-hits-3-8-trillion/. Published February 2, 2014. Accessed December 6, 2014.

3. Duke Department of Medicine website. http://medicine.duke.edu/faculty/details/0373417. Accessed December 4, 2014.

4. Cancer diagnosis puts people at greater risk for bankruptcy [press release]. Seattle, WA: Fred Hutchinson Cancer Research Center; May 15, 2013. http://www.fredhutch.org/en/news/releases/2013/05/cancer-diagnosis-greater-risk-bankruptcy.html.

Care Plans to Reduce Healthcare Utilization in Sickle Cell Disease

Surabhi Dangi-Garimella, PhD

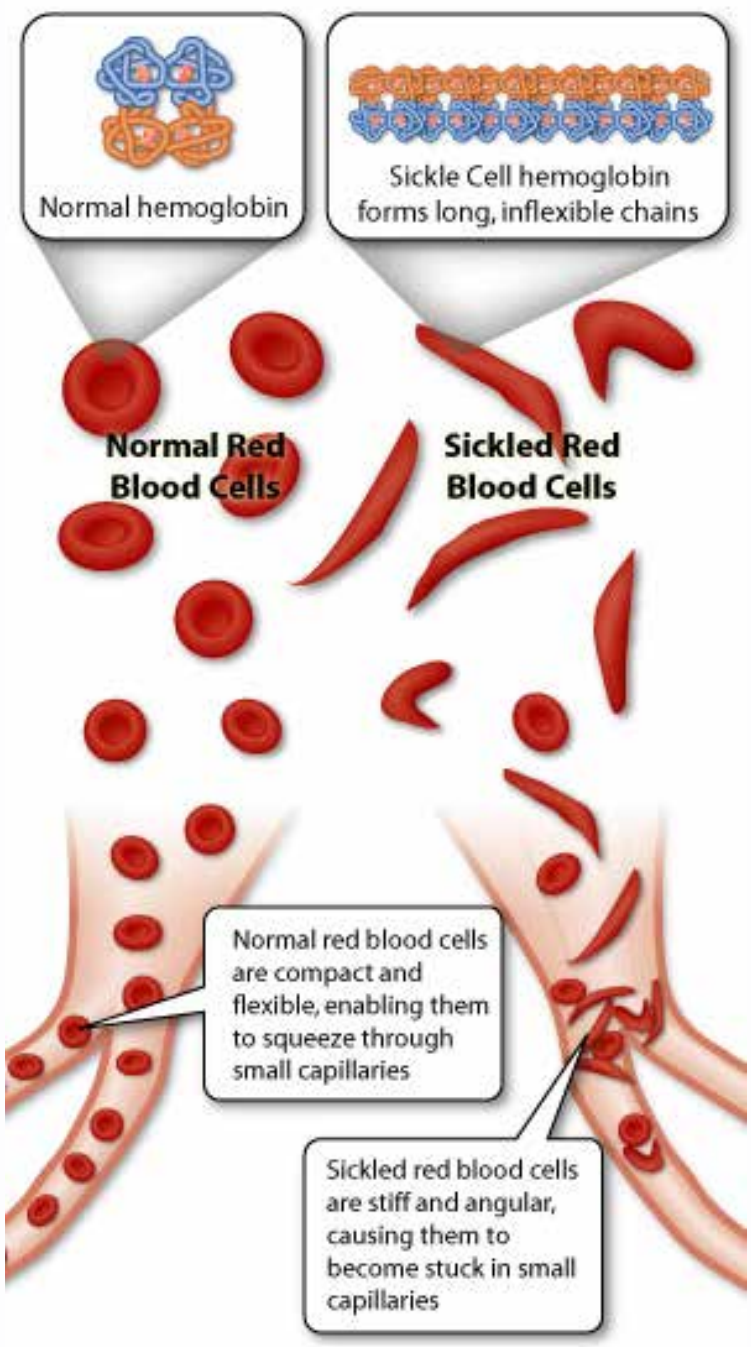
While innovations in drug development improve patient health, care management plans in hospitals and academic health institutes are evolving simultaneously to allow for better patient care at reduced costs. That was the conclusion of presenters at a Health Services and Outcomes Research session on sickle cell disease (SCD) management, part of the 56th Meeting of the American Society of Hematology, held in San Francisco, California, December 6-9, 2014.

SCD, a commonly inherited blood disorder resulting from abnormal hemoglobin, is associated with lifelong disabilities and can reduce life expectancy. The disease affects between 90,000 and 100,000 people in the United States,[1] and a study published in 2009 in the *American Journal of Hematology* estimated that the annual cost of medical care alone for these patients exceeds $1.1 billion.[2]

Jane S. Hankins, MD, MS, associate professor, St. Jude Children's Research Hospital, presented the model being evaluated at her institute to manage the transition of pediatric patients with SCD into adult care while avoiding the overutilization of healthcare.

Hankins explained that while most children with SCD survive into adulthood, healthcare utilization (HCU) is highest following transfer to adult care. Episodes of acute care or emergency department (ED) visits and hospitalizations are the primary drivers of these costs, she said. A review of HCU for SCD from ED visits and inpatient care in 8 states has previously shown that young adults (18 to 30 years old) are more than twice as likely to visit the ED as patients aged 10 to 17 years or adults aged 31 to 45 years. Young adults also have more inpatient stays and the highest percentage of frequent acute care visits.[3] Hankins pointed out that disease progression alone was not responsible for the upsurge in HCU. She rationalized that the failure to establish a suitable medical home following pediatric care is also a driver of higher HCU.

FIGURE. Hemoglobin in Sickle Cell Patients Is Inflexible, Resulting in the Abnormal Shape of Red Blood Cells



SOURCE: Sickle cell disease. University of Utah Health Sciences website. http://learn.genetics.utah.edu/content/disorders/singlegene/sicklecell/. Accessed December 12, 2014.

At St. Jude, independent SCD programs—1 adult and 1 pediatric—partnered to create the Young Adult Transition Clinic (YATC) in January 2012 for patients aged 18 to 25 years.[4] YATC became the model for addressing inadequate placement of young adults into adult care. The YATC at the St. Jude-Methodist Sickle Cell Disease Transition Clinic is located at the adult hospital and signifies 2 levels of overlap between pediatric and adult care: 1) comanagement by a pediatric hematologist and an internist, and 2) case management by a designated registered nurse coordinator in the pediatric setting at age 17 years, which continues in the adult setting up to age 25 years.[4] When asked why the age limit is 25 years when young adults can transition into adult care as late as 30 years of age, Hankins explained that the cutoff was limited by the fact that there was only a single RN available. All visits followed a detailed plan of care, including systematic orientation to adult care, disease-related education, and self-management strategies, she said.

The research group at YATC estimated the incidence rates (IRs) and incidence rate ratios (IRR) for HCU and health maintenance visits for the 2-year interval preceding departure from pediatric care, and the first 2 years following transfer to adult care, using a repeated measures model for HCU counts. They used a disease-specific survey on SCD pain management, before (pre-score) and immediately after (post score) an educational session by the nurse coordinator during both pediatric and adult care. These health literacy results were then compared using Wilcoxon signed rank test.[4]

Over a period of 2.5 years, between January 2012 and July 2014, 59 young adults (median age 16.3 years at the beginning of the observation period) with SCD initiated care at YATC within 3 months of leaving pediatric care. These patients were exposed to pediatric care for 2 years (median) and to adult care for 1.9 years (median). Hankins showed that while the IRR for HCU between pediatric and adult care did not change significantly, IRR for health maintenance visits decreased from 6.31 in pediatric to 4.28 during adult care, and a significant reduction in the 30-day readmission rate, from 33% to 23%, was observed following transfer to adult care, without any influence on the length of hospitalization. While health literacy definitely improved in both pediatric and adult care, pre-scores were significantly higher during adult care than during pediatric care (80% vs 90%; $P < .0001$), without a significant decline in scores in the mean 12 months after the pediatric (post score) and before the adult educational session (pre-score) (100% vs 90%; $P = .12$).[4] According to Hankins, this was a definite indicator of knowledge retention. "The overall attrition rate for YATC was 8.5%; we lost 1 patient to follow-up, while 4 patients were transferred to another provider for insurance policy change or following a personal request. There was 1 death due to multi-organ failure," she revealed.

Hankins emphasized that their medical home model at YATC was able to successfully prevent the expected upsurge in HCU and increase in 30-day readmission rate; it promoted medical literacy levels, and prevented high hydroxyurea utilization. She concluded that the long-term effectiveness of this medical home model could be demonstrated with continued longitudinal follow-up studies.

Deepa Manwani, MD, director of the Sickle Cell Disease Program of the Children's Hospital at Montefiore (CHAM) and an associate professor of clinical pediatrics at the Albert Einstein College of Medicine, presented the subsequent talk, which detailed a care plan to follow during hospital admission and at inpatient to outpatient discharge, with the aim of reducing HCU.

Hospital readmission has, today, become a quality-of-care indicator for numerous chronic conditions, and can be leveraged to reduce excessive healthcare costs.[5] A brief issued by the Agency for Healthcare Research and Quality found that 1 in 5 cases for most of the commonly treated conditions in hospitals saw readmission within 30 days. These include congestive heart failure (24.7%), schizophrenia (22.3%), and unspecified renal failure (21.7%). With SCD, the report suggests, at least 1 in 4 patients were readmitted at a rate of 31.9%, and interventions are ongoing at the state and national levels to reduce the incidence of and expenses resulting from readmissions.[6]

According to Manwani, multiple factors contribute to the high utilization rate, and not all are modifiable. Increasing age and psychosocial comorbidities are associated with a greater length of hospital stay (LOS), said Manwani, and she identified 18-to-30-year-old patients (as was presented by Hankins), public insurance, and admissions for pain crisis as some of the risk factors associated with a higher 30-day readmission rate. Studies have shown that SCD readmission rates could be greatly reduced by adequate outpatient follow-up with a trained hematologist on hospital admission,[7] along with written discharge management guidelines and intensive patient and provider education by a nurse educator.[8]

"Recruiting additional personnel could help, but it was not feasible for our practice," said Manwani. "So we arrived at a hypothesis that implementation of an individualized, multimodal care plan during inpatient stay and at inpatient to outpatient discharge will reduce acute care utilization." She added that implementing the comprehensive care plan at this key transition point was expected to be more effective due to:

- greater psychological readiness in the patient/family to accept escalation of care soon after an acute event
- decreased instances of "missed opportunities" in the event that the patient does not follow up with a provider with sickle cell–specific expertise
- improvement in communication among inpatient providers, outpatient providers with specific hematology expertise, and the multi-disciplinary team.

The SCD program at CHAM then worked on developing an SCD Quality Improvement Team, which met weekly to discuss and improve each patient's plan of care and interventions, she said. The team included representatives from the inpatient team, the primary hematologists, nursing, social work, psychology, and pain management. The primary end points to be achieved were reducing the 30-day readmission rates and LOS, while secondary end points included admission rates, ED return rates, and cost savings. "Our efforts were directed at consistent and comprehensive implementation of best practice guidelines, improved pain management strategies, a multimodal approach to patient care, and utilization of the hospital admission as an opportunity to design a comprehensive care plan," said Manwani. The study design compared data from 3.5 years before to 1 year after the initiation of the transition intervention.

The program was definitely successful, based on the results presented by Manwani. The analysis identified a significant reduction in LOS by 10% and 30-day readmission rate reduced by 38%. These results were even more significant in the 18-to-21-year age group. The team did not observe any concurrent increase in ED visits (3 and 7 days), and, more significantly, a reduction in the 3-day ED return rate in older patients was discerned. **EBO**

References

1. Sickle cell disease. CDC website. http://www.cdc.gov/ncbddd/sicklecell/about.html. Updated January 16, 2014. Accessed December 10, 2014.

2. Sickle cell disease healthcare costs high in US. Reuters website. http://www.reuters.com/article/2009/07/03/us-sickle-cell-idUSTRE5623EL20090703. Published July 3, 2009. Accessed December 11, 2014.

3. Lebensburger JD, Bemrich-Stolz CJ, Howard TH. Barriers in transition from pediatrics to adult medicine in sickle cell anemia. *J Blood Med*. 2012;3:105-112.

4. Hankins JS, Anderson S, Smeltzer MP, et al. A medical home model with overlap of pediatric and adult care mitigates the upsurge in health care utilization post-transfer to adult care in sickle cell disease. *Blood*. 2014;124(21):abstract 443.

5. Berry JG, Hall DE, Kuo DZ, et al. Hospital utilization and characteristics of patients experiencing recurrent readmissions within children's hospitals. *JAMA*. 2011;305(7):682-690.

6. Elixhauser A, Steiner C. Readmissions to U.S. hospitals by diagnosis, 2010. Agency for Healthcare Research and Quality website. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb153.pdf. Published April 2013. Accessed December 12, 2014.

7. Leschke J, Panepinto JA, Nimmer M, Hoffmann RG, Yan K, Brousseau DC. Outpatient follow-up and rehospitalizations for sickle cell disease patients. *Pediatr Blood Cancer*. 2012;58(3):406-409.

8. Frei-Jones MJ, Field JJ, DeBaun MR. Multi-modal intervention and prospective implementation of standardized sickle cell pain admission orders reduces 30-day readmission rate. *Pediatr Blood Cancer*. 2009;53(3):401-405.

Session on Survivorship Outlines Surveillance Strategies in Non-Hodgkin Lymphoma

Mary K. Caffrey

To scan or not to scan? Christopher R. Flowers, MD, MS, associate professor of hematology and oncology, Emory University School of Medicine, gave an overview of current thinking on when computed tomography (CT) and positron emission tomography scans still make sense to identify relapse in patients who had achieved a complete response (CR) in non-Hodgkin and other forms of lymphoma.

Flowers' presentation on December 7, 2014, at the 56th Annual Meeting of the American Society of Hematology (ASH), convening at the Moscone Center in San Francisco, California, was part of an education session, "Survivorship in Hematologic Malignancies." This presentation, however, had the greatest relevance for managed care, and came as ASH is drawing attention to unnecessary imaging.

As he and his coauthor, Jonathan B. Cohen, MD, noted in a companion paper to the session, surveillance imaging "is costly, may expose patients to minimal risks of mortality due to radiation-related secondary malignancies, and can lead to false-positive findings, leading to unnecessary biopsies."[1]

But the most practical problem with the use of routine scans after the second year of CR, Flowers said, is that they catch only a very small portion of relapses; after year 2, most cases of relapse are discovered due to the onset of clinical symptoms. In fact, he noted, ASH included routine scans as an area that needed improvement in its *Choosing Wisely* initiative, part of the ABIM Foundation campaign to reduce unnecessary tests and procedures for the benefit of patients. Among the studies Flowers cited:

- In a report of 117 patients with diffuse large B-cell lymphoma (DLBCL) who achieved CR to one of several non rituximab–containing combinations, 35 patients had a median follow-up of 4.6 years, including 7 who relapsed within 3 months of therapy. Just 2 had asymptomatic relapse identified solely by a routine scan.[1,2]
- A series of 100 relapsed patients with DLBCL, all of whom had CR/unconfirmed CR to initial therapy, reported that 22% of the relapses were identified based on routine scans and the rest were found through physical exams, symptoms, or laboratory tests. There was no significant difference in OS from time to relapse between the group identified by routine scans and those identified through other means.[1,3]

Close monitoring is not the issue, Flowers cautioned—only the use of scans. As he and Cohen wrote, "The majority of relapses in patients with aggressive NHL occur within the first 2 years, although up to 19% of patients merit continued close follow-up, even if imaging evaluations are not included. Patients should be encouraged to report any symptoms, and scans would certainly be used to investigate at that point."

On the flip side is the cost of imaging. Flowers presented a chart showing various costs per death avoided using surveillance CT scans every 6 months for 2 years, which is the current recommendation, or every 3 months for 2 years, then every 6 months until the 5-year mark for various rates of risk reduction. If risk is reduced 5%, and 112 deaths are avoided, the cost per death avoided for the first scanning protocol would be $181,210, while the cost for the second protocol would be $634,236.

Moving away from routine imaging in follow-up care for patients who have achieved CR makes the other tools of the hematologist more important than ever, Flowers said. "Good clinical judgment remains the cornerstone of patient care," he said. **EBO**

References

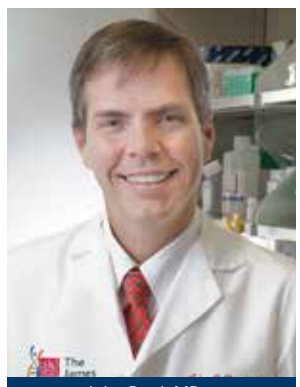
1. Cohen JB, Flowers CR. Optimal disease surveillance strategies in non-Hodgkin lymphoma. *Hematology*. 2014;2014:481-487.

2. Guppy AE, Tebutt NC, Norman A, Cunningham D. The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2003;44(1):123-125.

3. Lin TL, Kuo MC, Shih LY, et al. Value of surveillance computed tomography in the follow-up of diffuse large B-cell and follicular lymphomas. *Ann Hematol*. 2012;91(11):1741-1745.

ASH Presents Second Round of Tests, Treatments to Question Under *Choosing Wisely* Initiative

Mary K. Caffrey


John Byrd, MD


George R. Buchanan, MD


Mark Crowther, MD, MSc


Adam C. Cuker, MD, MS


Cindy R. Neunert, MD

Hematologists received recommendations about how long to use anticoagulants, when to transfuse sickle cell patients, and when to perform surveillance scans in patients with early stage chronic lymphocytic leukemia (CLL), as the American Society of Hematology (ASH) issued its second list of tests and treatments to question under the *Choosing Wisely* initiative.

This year's list was announced at the start of the 2014 Annual Meeting of ASH that convened at the Moscone Center in San Francisco. The first round of recommendations, numbers 1 through 5, were announced December 4, 2013, at the last ASH meeting in New Orleans. Details of recommendations 6 through 10 were presented at a session December 8, 2014.

Choosing Wisely is the initiative of the American Board of Internal Medicine Foundation that asks each specialty to identify tests or treatments that might be overused and unnecessary, with the potential to harm patients. While saving healthcare dollars is not the only consideration of *Choosing Wisely*, its efforts will have that effect if patients and their doctors are more judicious in their medical decisions.

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The 2014 ASH *Choosing Wisely* recommendations are:

- **Don't use anticoagulants for more than 3 months in patients with a first venous thromboembolism (VTE) occurring in the setting of a major transient risk factor.** This was presented by Mark Crowther, MD, MSc, of McMaster University in Hamilton, Ontario, Canada, who described this recommendation as a basic calculation of benefit versus risk; a VTE triggered by a major event such as surgery presents a low risk for recurrence once the major event has passed and recovery has occurred, assuming adequate care and anticoagulant therapy. Subsequently, such patients have a low risk of thrombosis, "and have the same risk of bleeding as other patients." The ASH recommendation does not apply to VTE linked to non-major risks, such as pregnancy or travel-associated immobility.

- **Don't routinely transfuse patients with sickle cell disease for chronic anemia or an uncomplicated pain crisis without an appropriate clinical indication.** Presented by George R. Buchanan, MD, of the University of Texas Southwestern in Dallas, this recommendation starts from the mandate, "First, do no harm." Unnecessary red blood cell transfusions can cause iron overload and other complications that require additional treatment, and unnecessary transfusions can make it difficult for sickle cell patients to find compatible blood supplies when they are truly needed. Buchanan said it is critical to ask: is this a routine transfusion specific to a clinical indication? What is the patient's gene type? As he discussed, and the companion paper in *Hematology* notes, stable patients with severe disease "can have baseline hemoglobin values between 7 and 10 g/dL and can tolerate 1 to 2 g/dL decreases without developing symptoms of anemia."[1] Most importantly, Buchanan said, using transfusions for chronic pain management does not work.

- **Don't perform baseline or routine surveillance computed tomography (CT) scans in patients with asymptomatic, early-stage CLL.** This recommendation incorporates a theme heard this year at ASH about overuse of scans, which has been a broad theme across managed care and cancer care especially. John Byrd, MD, of Ohio State University discussed this item, which states that in these circumstances of CLL, a CT scan does not improve survival for either staging or prognostic purposes. If anything, scans uncover incidental, irrelevant findings that drive up costs. The ASH recommendation calls for blood monitoring, and Byrd was among the speakers at ASH who urged clinicians to counsel patients about the value of biomarkers instead of radiation.

- **Don't test or treat for suspected heparin-induced thrombocytopenia (HIT) in patients with a low pre-test probability.** Adam C. Cuker, MD, MS, of the University of Pennsylvania, described the "4T" score, a widely used system that allows clinicians to evaluate the timing of a degree of thrombocytopenia and whether it might be caused by heparin. Cuker said this is one of the tough calls in medicine: for one, a patient is taken off heparin, and other anticoagulants are much more expensive. What's more, taking the test brings the risk of a false positive. Even if that turns out to be incorrect, once that information lands in a patient's file, it can be difficult for the patient to receive heparin again. Thus, Cuker emphasized the importance of not only not treating, but not testing for HIT, unless scores call for it.

- **Don't treat patients with immune thrombocytopenic purpura (ITP) in the absence of bleeding or low platelet count.** Cindy R. Neunert, MD, of Georgia Regents University, noted that this ASH recommendation applies to adults, and that pediatric cases have difficult criteria. In all cases, treatment should be aimed at improving quality of life without exposing patients to unnecessary risks and is always conditioned on prior bleeding episodes, activity levels, and social factors. In general, ITP treatment is rarely indicated in adults if platelet counts are above 30,000/microL unless they are facing surgery or other invasive procedures. **EBO**

Reference

1. Hicks LK, Bering H, Carson KR, et al. Five hematologic tests and treatments to question. *Hematology.* 2014;2014:599-604.

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Early Treatment, Monoclonal Antibodies Discussed in Multiple Myeloma

Mary K. Caffrey

Those who treat patients with multiple myeloma have witnessed a sea change in the past 15 years. Yet another revolution appears right around the corner, with research on risk stratification revealing how to identify who should be treated early. Promising results are expected on monoclonal antibodies, said Jesus F. San Miguel, MD, PhD, of the Clinica Universidad de Navarra in Pamplona, Spain.

Jesus F. San Miguel, MD, PhD

On December 6, 2014, San Miguel delivered the Han-Wasserman Lecture, "Multiple Myeloma: A Modern Model for Scientific and Clinical Progress," at the 56th Annual Meeting of the American Society of Hematology (ASH), which convened at the Moscone Center in San Francisco, California.

During his lecture, San Miguel previewed results that came later in the meeting on daratumumab, which targets CD38. Daratumumab, which received FDA breakthrough status in May 2013, and elotuzumab, which gained the status in 2014, have been highly anticipated by multiple myeloma patients and the clinicians who treat them. One of San Miguel's slides said results showed improved survival of 30% to 35% for daratumumab as a single agent, and 64% to 75% of patients in combination with lenalidomide and dexamethasone.

San Miguel said it has become clear that the disease "should not be considered a single entity, but different entities," and thus, multiple treatment options will exist. For example, he said, many thought there would be no role for melphalan after the 2013 ASH meeting in New Orleans, which saw the paradigm-shifting results from Thierry Facon, MD, on lenalidomide and low-dose dexamethasone. But San Miguel said that despite those results, melphalan remains a viable treatment option.

The talk opened with an overview of the increased understanding of the genetics behind myeloma, which is building awareness that treatments must be tailored to the individual. Identifying and measuring key "drivers" of the disease holds great promise, San Miguel said, as this will give clinicians the information to create combination therapies for more patients. While survival has increased from the abysmal rates of 1 to 3 years of years past to 5 to 7 years today, more can be done, he said.

San Miguel spent considerable time on an area where his group, the Spanish Myeloma Group, made a major contribution in 2013: risk-stratification of those precancerous patients who show signs of "smoldering" myeloma, and identifying for early treatment those at highest risk of developing the disease.

He was the senior investigator of the phase 3 trial published in the *New England Journal of Medicine*, in which patients were randomized to be treated with lenalidomide and dexamethasone or observation, the latter being the usual standard of care for patients who have an increase of plasma cells in the bone marrow that produce the monoclonal immunoglobulin, but do not have any symptoms. San Miguel outlined the prognostic factors that allowed the research team to segment out the high-risk group. "You want to give the patient what is needed, and nothing more than is needed," he said.

These results produced improved 3-year survival rates among the high-risk patients identified and treated by the Spanish team: 94% of the treated group was still alive at 5 years, compared with 78% in the untreated group.[1]

While most of his talk involved cutting-edge science, San Miguel ended on a highly personal note. He thanked his research team in Spain, his family, and especially his wife for many sacrifices. A final slide was a photo of a popular Spanish football team, with faces of his colleagues replacing those of the star players. He thanked the patients, and their families, and the pharmaceutical leaders who have contributed to the revolution in treating multiple myeloma. "This is why we become doctors; this is the reason why we are hematologists," he concluded. **EBO**

Reference

1. Spanish Myeloma Group study a treatment milestone. CenterWatch Newsline. http://www.centerwatch.com/news-online/article/5124/spanish-myeloma-groupstudy- a-treatment-milestone#sthash.bo7URvWm.dpbs. Published August 5, 2013. Accessed December 5, 2014.

Promising Results for Elotuzumab Presented in Session on Multiple Myeloma

Mary K. Caffrey

In March 2014, Dana Farber Cancer Institute's Kenneth C. Anderson, MD, raised expectations at the annual gathering of the National Comprehensive Cancer Network when he said it wouldn't be long before patients and clinicians in multiple myeloma (MM) practice would have "a monoclonal antibody or 2," the new class of therapy that trains the patient's immune cells to attack the cancer.

Based on the results presented at the 56th Annual Meeting of the American Society of Hematology (ASH) in San Francisco, Anderson's prediction is right on schedule. On December 8, 2014, Anderson's colleague at Dana Farber, Paul G. Richardson, MD, presented final results from a phase 1b/2 study of elotuzumab in combination with lenalidomide and dexamethasone for relapsed/refractory MM patients, including 73 who had already been treated with an average of 2 other therapies.[1]

Paul G. Richardson, MD

Results show highly encouraging overall response rate (ORR) and progression-free survival (PFS), with the responses even better at the lower dose of 10 mg/kg of elotuzumab than the higher dose of 20 mg/kg. However, during the question-and-answer period Richardson warned, "We have to be careful how we interpret that."

Elotuzumab, given by intravenous infusion, is being developed by Bristol-Myers Squibb in collaboration with AbbVie. The therapy binds to signaling lymphocytic activation molecule F7 (SLAMF7), giving it a different mechanism of action from other monoclonal antibodies under study, daratumumab and SAR650984, which target the CD38 protein. These therapies were stars at ASH 2014, with studies spotlighted in a press conference and a major lecture at the conference. The FDA granted breakthrough therapy status to the combination of elotuzumab with lenalidomide and dexamethasone in May 2014, based on promising phase 1 results. Daratumumab gained breakthrough status in May 2013 as a single agent.[2]

The phase 2 study included patients who had 1 to 3 prior therapies, including those with at least 1 prior therapy from the phase 1 study; their median age was 63 years. Half the patients received 10 mg/kg of elotuzumab, while the other half received 20 mg/kg of the drug, and treatment was in 28-day cycles. Patients also received oral lenalidomide at 25 mg for days 1 through 21 and oral dexamethasone (28 mg, plus 8 mg on days when the elotuzumab was given). This pretreatment was designed to manage infusion reactions.

Notably, ORR were 92% among patients in the 10-mg/kg group who responded to treatment compared with 76% for those in the 20-mg/kg group.

Median PFS was 32 months for the 10-mg/kg group and 25 months for the 20-mg/kg group.

A stringent complete response or complete response was observed in 14% of patients, with a very good partial response seen in 43%; another 27% had a partial response. Richardson said researchers were struck by both the quality and durability of these responses. "It's important to see, because many patients were on therapy for a number of years," he noted.

Common adverse events were diarrhea (66%), which Richardson described as manageable; fatigue (56%); muscle spasms (62%); constipation (51%); nausea (48%); and upper respiratory tract infections (47%). **EBO**

References

1. Richardson PG, Jagannath S, Moreau P, et al. Final results for the 1703 Phase 1b/2 study of elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood*. 2014;124 (21): abstract 302.

2. Elotuzumab receives breakthrough therapy designation for multiple myeloma. http://www.myelomabeacon.com/news/2014/05/19/elotuzumab-breakthrough-therapy-designation-multiple-myeloma/. Published May 21, 2014. Accessed December 17, 2014.

Sessions Report Phase 2 Results of Pomalidomide Combinations

Mary K. Caffrey

Results from a pair of phase 2 studies involving pomalidomide were reported December 8, 2014, during oral abstract sessions on treatments for multiple myeloma, as researchers continue to develop new combinations for patients who have stopped responding to earlier treatments.

Pomalidomide, an immunomodulatory drug marketed as Pomalyst, received FDA approval in February 2013 for multiple myeloma patients whose disease is demonstrating progression despite having had at least 2 other therapies, including lenalidomide and bortezomib.[1]

Results presented featured 2 combinations. A phase 1/2 study found pomalidomide with bortezomib and dexamethasone to be highly effective, with confirmed responses over 80%.[2] A second study determined that pomalidomide with cyclophosphamide and dexamethasone was superior to pomalidomide and dexamethasone only.[3]

Martha Q. Lacy, MD

Pomalidomide, bortezomib, and dexamethasone. Martha Q. Lacy, MD, of the Mayo Clinic, presented results involving 50 patients who had previously been treated with 1 to 4 therapies (median 3) and were not responding to lenalidomide.[2] The median age of the patients was 66 years; 51% were female. The median time from diagnosis to the time of the study was 46 months, and 68% had received a stem cell transplant.

Dosing was as follows: in phase 1, 9 patients started on 4 mg of pomalidomide on days 1 to 21, bortezomib 1 mg/m^2 weekly, and 40 mg of dexamethasone weekly. For 6 patients, dosing of bortezomib was increased to 1.3 mg/m^2, and this dose level was adopted for the larger group of patients in phase 2.

At 9 months, 72% of the patients were progression free, 96% were alive, and 66% continued treatment. Common adverse events (AEs) were anemia, fatigue, leukopenia, and thrombocytopenia, with the majority grade 1/2. AEs grade 3 and higher and their total occurrences were neutropenia (29) leukopenia (15), lung infection (6), lymphopenia (8), dyspnea (3), and syncope (3). Pulmonary embolism occurred in 1 patient. Among the 42 patients who could be evaluated, confirmed responses were seen in 34, including 9 of 11 high-risk patients. Median progression-free survival (PFS) was 17.7 months.

TREATMENT WITH AND WITHOUT CYCLOPHOSPHAMIDE.

Previously reported results of pomalidomide with dexamethasone had an overall response rate (ORR) of 33% and median PFS of 4.2 months in patients who had previously been treated with bortezomib and lenalidomide. This phase 2 trial involving 70 randomly assigned patients compared 1 arm of patients receiving the pomalidomide-dexamethasone combination (median age, 63 years) with a second arm also receiving cyclophosphamide (median age, 64 years).[3]

Dosing of dexamethasone was adjusted by age, and patients not receiving cyclophosphamide were allowed to cross over to join that arm if their disease progressed. After a median follow-up of 15 months, ORR (partial response or better) for the arm receiving pomalidomide and dexamethasone was 39%, while it was 65% for the arm also receiving cyclophosphamide. Clinical benefit (minimal response or better) was 64% for pomalidomide plus dexamethasone and 79% for the combo plus cyclophosphamide. Median PFS was 4.4 months compared with 9.2 months for the 2 arms, respectively. Grade 3/4 AEs were more frequent in patients receiving cyclophosphamide, although the authors reported that these were not statistically significant.

While the study ended in March 2014, the authors reported that as of July 2014, 28 of the original 70 patients had died—16 who did not start out in the arm receiving cyclophosphamide and 12 who did. During the study, 13 patients crossed into the second arm. **EBO**

References

1. Shilane J. Pomalyst: questions and answers about the FDA approval. The Myeloma Beacon. http://www.myelomabeacon.com/news/2013/02/13/pomalyst-pomalidomide-questions-and-answers-fda-approval/. Published February 13, 2013. Accessed December 9, 2014.

2. Lacy MQ, LaPlant BR, Laumann KM, et al. Pomalidomide, bortezomib, and dexamethasone (PVD) for patients with relapsed lenalidomide refractory multiple myeloma (MM). *Blood*. 2014;124(21):abstract 304.

3. Baz R, Martin TG, Alsina M, et al. Pomalidomide, cyclophosphamide, and dexamethasone is superior to pomalidomide and dexamethasone in relapsed and refractory myeloma: results of a multicenter phase 2 study. *Blood*. 2014;124 (21):abstract 303.

ASH Honors MMRF's Giusti

The many options and drug combinations available to a patient diagnosed today with multiple myeloma would have been unimaginable in 1996, when 37-year-old pharmaceutical executive Kathy Giusti learned she had this blood disease, which at that time had a grim prognosis and treatments that hadn't changed in decades.

KATHY GIUSTI

With her twin sister, Karen Andrews, Giusti founded the Multiple Myeloma Research Foundation (MMRF), and with it came an entirely new approach to supporting cancer research and drug development. Giusti's business background and results-oriented approach dramatically accelerated the pace at which therapies for myeloma achieved FDA approval.

On December 7, 2014, the American Society of Hematology (ASH) honored Giusti for her work with its Outstanding Service Award. Giusti, now the MMRF's founder and executive chairman, was not in San Francisco, but spoke to the attendees in a moving video message. "Over the past 17 years, the MMRF has worked tirelessly with scientists, clinicians and pharmaceutical partners to improve the outcome for myeloma patients, and we continue to work together to accelerate a cure for this devastating disease."

MMRF president Walter Capone accepted the award on Giusti's behalf. **EBO**

CML Updates: Defining MMR and Results of the DASISION Trial

Surabhi Dangi-Garimella, PhD

Several research groups gathered at the 56th Annual Meeting of the American Society of Hematology in San Francisco discussed findings from trials conducted in patients suffering from chronic myelogenous leukemia (CML) to prevent disease progression to advanced stages. Their session, held December 7, 2014, was called "Chronic Myeloid Leukemia: Outcomes With TKI therapy."

Jorge E. Cortes, MD, deputy department chair, Department of Leukemia, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Center, Houston, presented results

from the DASISION trial. In his talk, "Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)," he reported the results of the final 5-year analysis of DASISION. As has been published earlier, patients with newly diagnosed CML-CP were randomized to receive dasatinib 100 mg once daily (n = 259) or imatinib 400 mg once daily (n = 260). The primary end point was confirmed complete cytogenetic response (cCCyR) by 12 months. Long-term efficacy and safety data from patients with the predefined minimum 5 years of study treatment were presented.

Cortes reported that 61% of dasatinib-treated patients and 63% of imatinib-treated patients were still on their initial study therapy at the end of the period. Cytogenetic and molecular response rates continued to be higher for dasatinib compared with imatinib (intent-to-treat population). The rate of cCCyR by 5 years was particularly higher with dasatinib when compared with imatinib (83% vs 78%, *P* =.187), as were the rates of major molecular response (MMR; BCR-ABL ≤0.1%; 76% vs 64%; *P* =.002) and MR4.5 (BCR-ABL ≤0.0032% IS;

42% vs 33%; *P* = .025) by 5 years.

Further, he showed data that confirmed the times to cCCyR (95% CI; HR = 1.46, *P* =.0001) and MMR (95% CI; HR = 1.54; *P* <.0001) in all randomized patients were faster with the dasatinib arm. Fewer CML-CP patients in the dasatinib cohort (4.6%) progressed to the accelerated phase (AP) and blast phase (BP) compared with imatinib (7.3%). However, 5-year progression-free survival (PFS) and overall survival (OS) rates were similar across treatment arms. Significantly greater number of patients on dasatinib achieved BCR-ABL ≤10% at 3 months (84%) compared with those on imatinib (64%). And among the patients who achieved BCR-ABL ≤10% versus >10% at 3 months, improved PFS, OS, and lower rates of transformation to AP/BP were maintained at 5 years for both drugs.

According to Cortes, although the number of mutations following 4 to 5 years of treatment increased slightly in dasatinib-treated patients, the spectrum of mutations remained the same.

"While adverse events for both arms were as we expected, the total incidence of pleural effusion continued to increase each year in dasatinib-treated patients," he said. Discontinuation of dasatinib due to pleural effusion occurred in only 15 patients. Arterial ischemic events were uncommon. However, cardiovascular (CV) ischemic events and transient ischemic attack were reported in 10 and 2 dasatinib-treated patients, respectively, while CV ischemic and peripheral arterial occlusive events were reported in 4 and 2 imatinib-treated patients, respectively.

Cortes concluded that at the end of 5 years, 100 mg of dasatinib once daily presented superior outcomes compared with 400 mg of imatinib once daily as initial therapy for CML. He based his conclusion on the faster time to cCCyR and MMR, with more patients achieving BCR-ABL ≤10% at 3 months, sustained higher cumulative rates of response, and a lower rate of disease progression. According to Cortes, "Dasatinib offers meaningful advantages for patients with newly diagnosed CML-CP and remains a standard of care in this setting."

Susanne Saussele, MD, University of Heidelberg, Mannheim, Germany, was also a participant in this session She discussed therapy goals for MMR in CML, based on the CML-Study IV. "We sought to evaluate a failure time point for MMR using data of the CML-Study IV, a randomized 5-arm trial designed to optimize imatinib therapy, alone or in combination. We also evaluated the optimal time point to achieve an MMR," said Saussele.

In the current European LeukemiaNet (ELN) recommendations, the optimal time point to achieve MMR is defined at 12 months after diagnosis of CML.[1] "Not achieving MMR is not recommended as failure by ELN," said Saussele. "So there are uncertainties about when CML therapy can be altered in patients not reaching MMR after 12 months."

In the study, patients with valid molecular analysis on MR4 level were randomly divided into a learning sample (LS) and a validation sample (VS). For the LS, MR2, MMR, and deep molecular remission levels (MR4 or deeper), monthly landmarks were defined between 1 and 5 years after diagnosis. A patient was considered to be in MR2, MMR, or MR4 from the first diagnosis of the corresponding remission level and could only change to a higher level of response. Patients were censored after a stem cell transplant. For the failure time point analysis, for each of the resulting 48 landmarks, a Cox model was used to define the time to progression with age and EUTOS score as additional prognostic factors.

Between 2002 and 2012, 1551 patients

were randomized to LS or VS and 1358 had a valid molecular analysis on the MR4 level. Of the 1228 evaluable patients, two-thirds were randomly allocated to the LS (n = 818) and one-third to the VS (n = 410). Percentage of patients in the LS with MR2, MMR, and MR4 or deeper at 1 year were 28%, 29%, and 14%, respectively, and at 5 years were 5%, 21%, and 71%, respectively. Forty-four patients of the LS reached MMR on second-generation tyrosine kinase inhibitors. Saussele identified a significant PFS advantage for patients in MMR (*P* =.018). 8 years following treatment, the probability of PFS for patients in MMR was 90.8% compared with 80.5% of patients not in MMR.


Jorge E. Cortes, MD

Saussele said that the results of their model show that an optimal time point to predict PFS in patients with MMR was defined at 2.25 years after diagnosis, which could be construed as being significant. Further, at any time point, patients in MMR had a lower risk of progression than patients not in MMR.

> *"Dasatinib offers meaningful advantages for patients with newly diagnosed CML-CP and remains a standard of care in this setting."*
>
> —JORGE E. CORTES, MD

"This model can help determine when MMR is a failure and when a change in therapy should be considered. However, we should be aware that the earlier MMR is achieved, the higher is the chance to achieve deep molecular response later during therapy," concluded Saussele. **EBO**

REFERENCE

1. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.

Poster Presentations Cover Therapeutic Options in CML

Surabhi Dangi-Garimella, PhD

A poster session December 7, 2014, at the 56th Annual Meeting of the American Society of Hematology in San Francisco was dedicated to trials evaluating therapeutic options in chronic myelogenous leukemia (CML). Data presented covered safety, efficacy, managing comorbidities, and biological differences that drive response to therapy.

One poster, "Long-Term Outcomes of First-Line Tyrosine Kinase Inhibitors for Chronic Phase Chronic Myeloid Leukemia: A Mixed-Treatment Comparison," summarized the efficacy and safety of tyrosine kinase inhibitors (TKIs), comparing them directly and indirectly, in the mature follow-up for patients with newly diagnosed chronic phase (CP)-CML.

The authors included data from randomized controlled trials evaluating TKIs in adults with newly diagnosed CP-CML. A TKI (imatinib, dasatinib or nilotinib) was included if used as an initial treatment. Studies on bosutinib were excluded, as it is only approved in the United States for the treatment of CP-CML after failure of initial therapy. Studies that included patients with accelerated- or blast-phase CML, intolerant or resistant patients to first-line treatment, those on IFN-α, older agents, or stem cell transplantation were excluded. Primary outcomes examined were efficacy, represented by major molecular response (MMR, ≤0.1% BCR-ABLIS) and deeper molecular responses (MR4.5, ≤0.0032% IS); survival, represented by overall survival and progression free survival; and safety, represented by medication discontinuation rate due to adverse events.

As available trials provided direct comparison with imatinib, with no head-to-head trials to compare other TKIs, the authors conducted a mixed treatment comparison (MTC) analysis, which pools evidence from direct and indirect comparisons to facilitate simultaneous inference regarding all treatments. Bayesian mixed-treatment comparison method was used to rank TKI in terms of effectiveness. The study identified 4 landmark trials, including the DASISION and ENESTnd trials, which included 1647 patients with CP-CML. Follow-up times ranged from 3 months to 6 years. MTC analysis on these reported trials demonstrated superiority of both nilotinib and dasatinib over imatinib in terms of efficacy and safety. Nilotinib ranked first in efficacy with better MMR and MR4.5 after a 2-year follow-up, followed by dasatinib. Dasatinib was observed to have the highest medication discontinuation rate due to adverse events or drug-related toxicity. Among TKIs, nilotinib was found to have the best survival profile, though statistically nonsignificant.

The authors concluded that both nilotinib and dasatinib are associated with significantly better efficacy and safety profiles compared to imatinib. After a 2-year follow-up, nilotinib ranked first to achieve MMR and MR4.5, with lower discontinuation rate due to adverse events. The authors conclude that new generation TKIs exhibit a faster and more potent response over a longer follow-up period.

Results of the PACE trial were also presented during this poster session; the study authors presented their data as the "Long-term follow-up of ponatinib efficacy and safety in the phase 2 PACE trial." The trial evaluated efficacy and safety of ponatinib (45 mg daily) in CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) patients who were resistant/intolerant to dasatinib or nilotinib or if they harbored the T315I mutation. The authors clarified that in October 2013, the trial was placed on partial clinical hold due to observation of arterial thrombotic events (ATEs) in the ponatinib clinical program, following which dose reductions were recommended. They now reported long-term follow-up analysis (minimum 23.9 month follow-up from last patient, first visit). For ATEs, exposure adjusted yearly incidence rates were calculated as (number of patients with first event in interval)/(total exposure for the interval)*100 [adverse events (AEs) per 100 patient years]. Rates for later intervals excluded patients with prior events.

Patients in this study group were heavily pretreated: 58% received more than 3 prior TKIs. Most common reasons for discontinuation were progressive disease (21%) and AEs. For CP-CML patients, 2-year major cytogenetic response (MCyR) duration, progression-free survival (PFS), and overall survival (OS) estimates were 87%, 67%, and 86%, respectively. For accelerated-phase (AP) CML, blast-phase (BP) CML, and Ph+ ALL, estimated OS at 3 years was 59%, 9%, and 16%, respectively. The study authors observed that responses were generally maintained after dose reduction: 99% maintained MCyR, 96% maintained complete cytogenetic response, and 90% maintained MMR. Frequent (≥20%) treatment-emergent AEs were thrombocytopenia (44%), abdominal pain (41%), rash (41%), constipation (37%), headache (37%), dry skin (35%), fatigue (29%), pyrexia (29%), nausea (28%), arthralgia (28%), hypertension (26%), neutropenia (25%), anemia (22%), myalgia (21%), diarrhea (21%), vomiting (21%), increased lipase (21%). Most common serious AEs were pneumonia (7%) and pancreatitis (6%). ATEs observed in 19% of patients included cardiovascular (10%), cerebrovascular (7%), and peripheral vascular (7%) events. Venous thromboembolic events were observed in 5% patients.

> *Results of the PACE trial showed that ponatinib continues to exhibit deep and durable responses in heavily pretreated patients with longer follow-up. However, a benefit-risk evaluation to guide the initiation of ponatinib therapy, particularly in patients who may be at an increased risk of ATEs, is recommended.*

The authors reported that after a 3-year follow-up, 22% of the CP-CML patients achieved MR4.5 and 83% remained in MCyR. PFS and OS at 3 years were 61% and 82%, respectively.

Based on their trial data, the authors conclude that ponatinib continues to exhibit deep and durable responses in heavily pretreated patients with longer follow-up, particularly CP-CML. They recommend a benefit-risk evaluation to guide the initiation of ponatinib therapy, particularly in patients who may be at an increased risk of ATEs. The authors plan to conduct a dose-ranging trial of ponatinib in refractory CML for benefit-risk evaluation. **EBO**

SPIRIT 2: Dasatinib Superior to Imatinib in Newly Diagnosed CML

Surabhi Dangi-Garimella, PhD

Results from a large phase 3 prospective randomized open-label trial comparing imatinib 400 mg daily with dasatinib 100 mg daily were presented by Stephen O'Brien, MD, professor of hematology, Newcastle University Medical School, Newcastle upon Tyne, England. He presented the results of SPIRIT 2, which compared the 2 drugs in patients with newly diagnosed chronic myelogenous leukemia, at the 56th Annual Meeting of the American Society of Hematology, held in San Francisco.

According to O'Brien, the SPIRIT 2 trial design was similar to the DASISION trial. The trial recruited 814 patients at 172 hospitals across England and in Northern Ireland between August 2008 and March 2013. The primary end point of the trial was event-free survival at 5 years. Key secondary end points listed in the trial were the rate of achievement of a major molecular response (defined as BCR-ABL/ABL ratio of less than 0.1%), cytogenetic response, and toxicity. The trial had an even distribution of patients between the 2 arms.

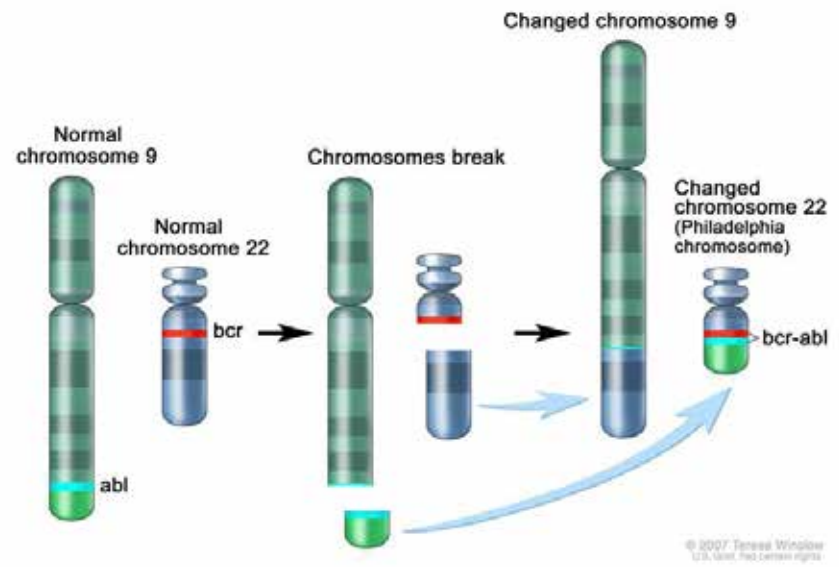
With a median follow-up of 37.4 months, O'Brien said 300 patients have discontinued the study medication: 170 in the imatinib arm (7 deaths while on treatment) and 130 in the dasatinib arm (5 deaths while on treatment). Following discontinuation, an additional 11 patients from the imatinib arm and 15 from the dasatinib arm died. The research group is currently following 124 of the patients in the imatinib arm and 89 in the dasatinib arm.

While there were no unexpected side effects observed, O'Brien said that patients receiving imatinib experienced GI toxicity more often than patients receiving dasatinib; fatigue, rash, and headache were more common with dasatinib. Also, a higher rate of grade 3/4 thrombocytopenia was observed in the dasatinib arm, pleural effusions occurred in 78 of 406 (19.2%) patients on dasatinib, and 13 of 78 (16.7%) patients required drainage. No significant differences in cardiovascular adverse events were observed, he noted.

While significant differences in major cytogenetic response and complete cytogenetic response were observed, with dasatinib presenting a better effect, O'Brien cautioned that a large amount of data was missing in this analysis. This could, in reality, render the difference insignificant.

O'Brien concluded that dasatinib-treated patients have a higher rate of molecular response at 1 year, but, with a median follow-up of 37.4 months, there is no significant difference in rates of disease progression or overall survival. He suggested the need for additional follow-up to evaluate differences in event-free survival at 5 years, if any. **EBO**

FIGURE. Philadelphia Chromosome in Chronic Myelogenous Leukemia



A characteristic chromosomal translocation observed between chromosome 9 and chromosome 22 results in the bcr-abl gene fusion on chromosome 22.

SOURCE: NCI website. http://www.cancer.gov/cancertopics/pdq/treatment/CML/Patient/page1#figure_158_e. Accessed January 7, 2015.

RESEARCH REPORT

Ibrutinib Demonstrates Significant Responses for Patients With Hard-to-Treat CLL/SLL, Phase 2 Data Show

Mary K. Caffrey

Patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) who show a deletion of the short arm of chromosome 17 (del 17p) typically see a rapid progression of their disease, with an average life expectancy of less than 2 years once the disease relapses or stops responding to treatment.

In the largest prospective trial dedicated to treating patients with this disease profile, ibrutinib showed marked efficacy in overall response rates, according to data presented December 8, 2014, at the 56th Annual Meeting of the American Society of Hematology held in San Francisco.

The study, led by Susan O'Brien, MD, involved 144 patients: 137 with CLL and 7 with SLL. All had del 17p, their median age was 64 years, and 63% were stage III or IV. Patients received 420 mg of oral ibrutinib once daily until progression; all patients receiving at least 1 dose were included in the analysis. The overall rate of response (ORR) was 82.6%, including 17.4% with partial response with lymphocytosis. Complete response with incomplete bone marrow recovery was reported in 3 patients. An Independent Review Committee-assessed ORR is pending.

At a median follow-up of 13 months, the median progression-free survival and duration of response by investigator determination had not been reached. However, at 12 months, 79.3% of the patients were alive and progression-free and 88.3% of the responders were progression-free. Progressive disease was reported in 20 patients.

The most frequent adverse events (AEs) were diarrhea (36%), fatigue (30%), cough (24%), and arthralgia (22%). Atrial fibrillation was reported in 11 patients. Seven patients reported basal or squamous cell skin cancer. One patient had plasma cell myeloma.

The most frequent grade 3-4 AEs were neutropenia (14%), anemia (8%), pneumonia (8%), and hypertension (8%). Major hemorrhage was reported in 7 patients, all grade 2 or 3, and 16 patients stopped therapy due to AEs, with 8 later having fatal events.

At the time of data cut off, median treatment duration was 11.1 months, and 101 of the 144 patients continued treatment with ibrutinib. **EBO**

REFERENCE

1. O'Brien S, Jones JA, Coutre S, et al. Efficacy and safety of ibrutinib in patients with relapsed and refractory chronic lymphocytic leukemia or small lymphocytic leukemia with 17p deletion: results from phase 2 RESONATE trial. *Blood*. 2014;124(21):abstract 327.

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Introducing the first and FDA-approved treatment

patients with polycythemia vera an inadequate response to or are

In a phase 3 trial of Jakafi® (ruxolitinib) vs best available therapy:

- 21% of patients receiving Jakafi achieved the primary composite end point of hematocrit (Hct) control and spleen volume reduction compared with <1% of patients on best available therapy at week 32 ($P < 0.0001$)*

Indications and Usage

Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

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 X 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
- 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

Incyte

only for who have had intolerant of hydroxyurea[1]

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
- 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 page.

Visit www.jakafi.com/HCP
to see Full Prescribing Information and learn more about Jakafi for use in PV

* A randomized, open-label, active-controlled phase 3 trial comparing Jakafi with best available therapy in 222 patients. Best available therapy included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). The primary end point was the proportion of subjects achieving a response at week 32, with response defined as having achieved both Hct control (the absence of phlebotomy eligibility beginning at the week 8 visit and continuing through week 32) and spleen volume reduction (a ≥35% reduction from baseline in spleen volume at week 32). Phlebotomy eligibility was defined as Hct >45% that is ≥3 percentage points higher than baseline or Hct >48% (lower value).

Reference: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation.

Jakafi®
ruxolitinib (tablets)

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)*]. 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)*]. **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.

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)*] • Risk of Infection [*see Warnings and Precautions (5.2)*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3)*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4)*]. 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 myelofibrosis patients in clinical studies with Jakafi, 52% were 65 years of age 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.

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Results Project Savings for Payers With Novel Oral Anticoagulants

Mary K. Caffrey

Payers in the United States would see a reduction in overall medical costs if patients switched to newer, novel oral anticoagulants, based on a study of 10 clinical trials involving dabigatran, rivaroxaban, and apixaban.

Results of the study were presented December 6, 2014, at a poster session on health services and outcomes research during the 56th Annual Meeting of the American Society of Hematology (ASH), which took place at the Moscone Center in San Francisco, California.

The study's lead author, Alpesh N. Amin, MD, MBA, consults for Bristol-Myers Squibb (BMS) and for Pfizer, joint makers of apixaban. The authors sought to review recent clinical trials for new oral anticoagulants and compare event rates for patients taking these newer therapies for nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE) with those taking standard therapy or placebo.

In this study, the authors started with treatment costs at the 2013 level and adjusted for inflation, with costs projected from 2014 through 2018. Projections were based on a hypothetical health plan of 1 million members, and prevalence of both conditions was derived from published literature. The authors assumed the same usage rate for all 3 newer therapies when making comparisons.

For 2014, a hypothetical health plan of 1 million insured lives would see medical savings of $3 million by using dabigatran, $2.1 million by using rivaroxaban, and $7.3 million by using apixaban for its NVAF patients.

For acute VTE, savings were $700,000 for dabigatran, $2.2 million for rivaroxaban, and $4.1 million for apixaban. Savings for the VTE patients for extended periods would be $6.3 million for dabigatran, $6.6 million for rivaroxaban, and for apixaban, $9.5 million for the 2.5-mg arm and $9.6 million for the 5-mg arm.

In 2014, savings for the combined NVAF and VTE populations are projected to be $10 million with dabigatran, $10.9 million with rivaroxaban, and $21 million with apixaban. Savings from 2015 through 2018 were projected to steadily rise for all 3 therapies, although the greatest savings relative to standard care would come in the earliest years of treatment. The authors recommend confirming the results in real-world settings.[1]

STUDIES ON SICKLE CELL DISEASE. Two presentations at the December 6, 2014, poster session concerned sickle cell disease (SCD), which received considerable attention at the 56th ASH Annual Meeting. The first examined patient and caregiver perspectives on adherence to iron chelation therapy (ICT), which is used to manage iron overload in patients with SCD and other anemias who have repeat transfusions. Interviews with 11 patients and 10 caregivers from 6 cities in the United States were coded through a consensus process. Children were not interviewed if they were younger than 9 years.

Respondents said reasons for adherence included perceived positive effects of ICT on health and longevity, support from caregivers and clinicians, and an established routine for taking treatment. Reasons for nonadherence included not liking the taste, or aftertaste, or texture of the therapy or its side effects, such as gastrointestinal symptoms. Mealtime restrictions were also an issue. Caregivers said children who had a better understanding of the benefits of treatment had better adherence and that adherence improved as children got older. Several coping mechanisms were reported, such as efforts to mask the taste. The lead author and all but 1 coauthor are employed by Novartis.[2]

A study based at the University of Wisconsin examined the impact of blood transfusion therapy on the quality of life on children with SCD. A group of 196 children in the Multicenter Silent Infarct Transfusion Trial were divided into 2 groups: those who received at least 18 months or more of transfusion (effectively transfused) and those who received less than 18 months. Parents or guardians completed assessments using the Child Health Questionnaire at baseline, at study exit, or at a neurological event. The group was 43% female with a mean age of 9.55 years, and 92% were African American. The groups were equal by gender, disease severity, and rates of pain. At study exit, results showed that children in the effectively transfused group had higher scores in the following areas:

- physical function (M = 12.68; SE = 3.52), t (174) = 3.61, $P \leq .001$;
- bodily pain (M = 13.16, SE = 3.74), t (174) = 3.51, $P \leq .001$;
- change in health (M = 0.39; SE = 0.14), t (166) = 2.71, P =.01.[3]

The authors described these results as the first evidence that blood transfusion improves health-related quality of life for children with SCD. Mast Therapeutics provided research funding for the study. **EBO**

References

1. Amin, AN, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Comparison of medical costs avoided when new oral anticoagulants are used for the treatment of patients with atrial fibrillation and venous thromboembolism in the US. *Blood*. 2014;124(21):poster 2181.

2. Bal V, Cote I, Lasch K, Huang V. Patient and caregivers perspectives of factors associated with adherence to and satisfaction with iron chelation therapy. *Blood*. 2014;124(21):poster 2166.

3. Beverung LM, Strouse JJ, Hulbert ML, et al. Health-related quality of life in children with sickle-cell disease: impact of blood transfusion therapy. *Blood*. 2014;124(21):poster 2167.

Study Suggests Method of Reducing Blood Clots Without Risking Bleeding

Mary K. Caffrey

It's long been assumed that clinicians who treat patients to avoid blood clots must risk consequences: the potential for bleeding. A study named one of the "Best of ASH" at the 56th Annual Meeting of the American Society of Hematology, and simultaneously published in the *New England Journal of Medicine*, works around that problem, and it could give clinicians a safer way to limit blood clots, with enormous safety potential for patients.[1]

Factor XI, an important enzyme in the coagulation pathway, is naturally reduced in some people, and this group is at a lower risk of venous thromboembolism, or VTE. So, the reasoning went, if Factor XI was reduced by other means in patients undergoing a surgical knee replacement—a procedure with high risk for blood clots—would the patients have reduced VTE?

First presented at a press conference December 7, 2014, and then at the late-breaking abstract session December 9, 2014, the study led by Harry Büller, MD, PhD, of the Academic Medical Center of the University of Amsterdam, the Netherlands, described how researchers used injectable nucleic acid engineered to reduce Factor XI expression.

At the press conference, Büller could barely contain his excitement about the results, and confessed he had grown weary of holding in his secret. "This is the holy grail," he said. The ability to decouple treatment for blood clots from bleeding episodes could revolutionize surgical care and reduce medical costs. His study was 1 of 4 related to blood clots discussed during the news conference, while efforts to control bleeding and hold down its related costs gained notice at ASH in 2014.[2]

In a randomized controlled trial, approximately 300 patients receiving total knee replacement received an interfering agent for Factor XI, in doses of either 200 or 300 mg, or the anticoagulant enoxaparin at 40 mg. Patients received subcutaneous injections of Factor XI starting 36 days before surgery, to allow time for the treatment to interfere with Factor XI production, with the last dose 3 days after surgery. Those in the control group received enoxaparin for 8 days after surgery.

Subsequently, patients receiving 300 mg of a Factor XI interfering agent had the lowest occurrence of VTE (4.2%, 3 of 71 patients) when compared to those receiving 200 mg of the Factor XI agent (26.9%, 36 of 134 patients) or enoxaparin (30.4%, 21 of 69 patients). Also, those who received the Factor XI interfering agent had fewer bleeding incidents than those who had enoxaparin (bleeding rate of 2.6% in the high-dose Factor XI agent group compared with 2.8% in the low-dose group and 8.3% for anticoagulant group.) Researchers found the Factor XI interfering agent did not

increase bleeding and did not interfere with other aspects of coagulation.

BLOOD CLOTS AND CANCER. A pair of studies involving blood clots and cancer were presented at the December 7, 2014, press conference. Data gathered by researchers from the Netherlands examined 926 cancer patients from 11 studies or registries who had lung scans for other reasons that recorded incidental pulmonary embolism (IPE). Researchers found that the chance of developing a second clot were nearly double in cancer patients with IPE who did not receive continued anticoagulant treatment, compared with those who had low-molecular weight (LMWH) heparins or vitamin K antagonists, or VKAs (12% compared with 6.2% or 6.4%). Six-month mortality was higher in untreated patients (47%) than in patients with LMWH or VKAs.[3]

Another study found that tinzaparin, a LMWH, was more effective than warfarin for treating actue VTE in cancer patients. The results discussed by Agnes Lee, MD, of the University of British Columbia in Vancouver, Canada, were also presented at the late-breaking session. They essentially confirm a single trial on which current guidelines are based. Lee explained that study participants received either tinzaparin once daily for 6 months or tinzaparin once daily for 5 to 10 days, followed by 6 months of warfarin. During the treatment period, 31 patients (6.9%) treated with tinzaparin experienced recurrent VTE compared with 45 (10%) patients treated with warfarin. Tinzaparin was only statistically significant in reducing recurrent VTE in veins above the knee. Researchers did not observe a difference in the mortality or incidence of major bleeding events (2.9% in the tinzaparin arm and 2.7% in the warfarin arm), but noted that significantly fewer patients experienced clinically relevant, non-major bleeding with tinzaparin than warfarin (11% vs 16%). Under questioning, Lee acknowledged that warfarin is significantly less expensive than tinzaparin and other LMWH, and press conference moderator Mary Cushman, MD, of the University of Vermont in Burlington, said that her hospital defaults to warfarin if patients cannot get insurance coverage for heparins.[4]

NOACS IN REAL-WORLD SETTINGS. Newer medications than warfarin, known as novel anticoagulants (NOACs), do cost more but require less monitoring to assess bleeding risk, and there is no recommended standardized dose. Three newer anticoagulants—dabigatran, apixaban, and rivaroxaban—may help patients avoid these other non medication costs. A study presented December 7, 2014, examined bleeding risks outside of a clinical trial setting. Martin H. Ellis, MD, of Meir Medical Center in Kfar Saba, Israel, presented a population analysis that looked at 18,249 patients with atrial fibrillation who took warfarin or a NOAC (dabigatran or rivaroxaban) between January 1, 2011, and December 31, 2013. Patients taking warfarin had 3.9 bleeding episodes per 100 patient years, while those taking dabigatran had 2.8 (150 mg twice daily) or 4.6 (110 mg twice daily), and 4.3 episodes on rivaroxaban. Ellis said the slightly higher bleeding rate on the lower dose was explained by doctors managing the doses of patients who started out with higher risks of bleeding. He noted that while the newer therapies present advantages, there are still risks, and patients and physicians must be alert.[5] **EBO**

References

1. Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* [published online December 7, 2014]. doi:10.1056/NEJMoa1405760.

2. Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *Blood*. 2014;124(21):poster LBA-1.

3. van der Hulle T, den Exter PL, Meyer G, et al. Risk of recurrent venous thromboembolism and major bleeding in cancer-associated incidental pulmonary embolism amongst treated and untreated patients: a pooled analysis of 926 patients. *Blood*. 2014;124(21):poster 590.

4. Lee AA, Kamphuisen PW, Meyer G, et al. Randomized trial of long-term tinzaparin, a low molecular weight heparin (LMWH), versus warfarin for treatment of acute venous thromboembolism (VTE) in cancer patients – the CATCH study. *Blood*. 2014;124(21):poster LBA-1.

5. Ellis, MH, Neumann T, Ginsberg, JS, et al. Bleeding in patients with atrial fibrillation treated with non vitamin K antagonist oral anticoagulants: a population-based study. *Blood*. 2014;124(21):poster 343.

Best of ASH Presentations: Platelets, Lenalidomide for MDS, and Sorafenib in AML

Surabhi Dangi-Garimella, PhD

Research on platelets, on lenalidomide in myelodysplastic syndrome (MDS) and sorafenib in acute myeloid leukemia (AML), highlighted the plenary session held December 7, 2014, at the 56th Annual Meeting of the American Society of Hematology (ASH) in San Francisco. Presentations at the session were selected by the Program Committee from among the thousands of scientific abstracts that were accepted for the meeting.

Renata Grozovsky, PhD, a research fellow at Brigham and Women's Hospital, Boston, delineated an in vitro and in vivo mechanism, regulated by the JAK2-STAT3 signaling pathway, which regulates platelet production. Thrombopoietin (TPO) was discovered in 1958 but only identified as a ligand of the c-MPL receptor in 1994. While TPO is a well-studied regulator of platelet production, supporting the survival, proliferation, and differentiation of platelet precursors, and bone marrow megakaryocytes, mechanisms regulating circulating TPO levels have been a topic of debate, Grozovsky said. Through a collaboration with scientists across Brigham and the Department of Biotechnology, University of Rijeka, Croatia, Grozovsky provided evidence that platelets lacking sialic acid (desialylated platelets) are removed by the hepatic Ashwell-Morell receptor (AMR), thereby regulating platelet survival and hepatic TPO levels.

"We hypothesized that clearance of desialylated platelets by AMR increases TPO in the liver," said Grozovsky. Her research team found that preventing the expression of the asialoglycoprotein receptor (Asgr2) subunit of AMR in mice improved platelet survival compared to the control mice. In fact, $Asgr2^{-/-}$ mice had lower liver TPO mRNA levels, as well as expressed platelets that were desialylated. Mice lacking the sialyltransferase ST3GalIV, on the other hand, had an increase in liver TPO mRNA. Desialylated platelets isolated from $St3gal4^{-/-}$ or $Asgr2^{-/-}$ mice infused into WT mice increased hepatic TPO mRNA levels, plasma TPO levels, and bone marrow megakaryocytes. However, desialylated platelets infused into $Asgr2^{-/-}$ mice had no effect on TPO mRNA synthesis, TPO plasma levels, or bone marrow megakaryocyte numbers, researchers found.

To identify the underlying signaling mechanism, Grozovsky described conducting biochemical evaluation of the mouse liver cells and human HepG2 cells: within a half hour of ingesting desialylated platelets, increased phosphorylation of the tyrosine kinase JAK2 was observed in $St3gal4^{-/-}$ mice and a marked reduction in JAK2 phosphorylation in $Asgr2^{-/-}$ mice. "When we treated the cells with the JAK1/2-specific inhibitor, AZD1480, we observed reduced STAT3 phosphorylation and nuclear translocation, and reduced expression of both the TPO mRNA and protein in HepG2 cells incubated with desialylated platelets." The results were translated in vivo in mice; treating the control wild-type mice with AZD1480 blocked TPO mRNA induction by the desialylated platelets. Grozovsky concluded that clearance of aging desialylated platelets by AMR has a substantial clinical significance, considering that the JAK1/2 inhibitor often causes thrombocytopenia.

All the presentations during the plenary session were delivered by senior research investigators, with the exception of the talk by Emma Fink, an MD-PhD student in the laboratory of Benjamin L. Ebert, MD, PhD, Brigham and Women's Hospital, Boston. Her talk was titled "Lenalidomide induced ubiquitination and degradation of CSNK1A1 in MDS with del(5q)."

Lenalidomide is a highly effective treatment for multiple myeloma and MDS with deletion of chromosome 5q (del(5q)). Recent work from their laboratory and others demonstrated that lenalidomide activates the CRBN-CRL4 E3 ubiquitin ligase to ubiquitinate IKZF1 and IKZF3. Degradation of these lymphoid transcription factors explains lenalidomide's growth inhibition of multiple myeloma cells and increased IL-2 release from T cells. "We hypothesized that ubiquitination of a distinct CRBN substrate in myeloid cells could explain the efficacy of lenalidomide in del(5q) MDS," Fink stated.

She went on to describe quantitative proteomic experiments in the myeloid KG-1 cells, which identified casein kinase 1A1 (CSNK1A1), a novel target that had increased ubiquitination and decreased protein abundance following lenalidomide treatment. Csnk1a1, being encoded in the del(5q) commonly deleted region, is a potential lenalidomide target in del(5q) MDS.

"We validated that lenalidomide treatment decreased CSNK1A1 protein levels in multiple human cell lines in a dose-dependent manner without altering Csnk1a1 mRNA levels," said Fink.

Moreover, lenalidomide treatment increased ubiquitination of CSNK1A1 in cell lines. Previous work from Ebert's laboratory had shown that CSNK1A1 was a negative regulator of p53 and β-catenin. So their research group worked on the hypothesis that lenalidomide would induce degradation of CSNK1A1, resulting in the specific apoptosis of haploinsufficient del(5q) cells.

To tease out the mechanism, they conducted co-immunoprecipitation experiments, which pulled down CSNK1A1 with CRBN in the presence of lenalidomide, demonstrating a direct interaction of CSNK1A1 with the substrate adaptor for the ubiquitin ligase. Mixing CRBN-CRL4 with CSNK1A1 demonstrated in vitro ubiquitination of CSK1A1. These results were further validated in a genetically defined CSNK1A1 conditional knockout mouse model. While murine cells were found resistant to the effects of IMiDs, murine Ba/F3 cells overexpressing human CRBN (hCRBN), but not murine CRBN, degraded CSNK1A1 in response to lenalidomide. "This could explain why thalidomide, which was found responsible for acute teratogenicity in humans, failed to show any toxicity in mouse experiments," Fink explained. Finally, her group observed that CSK1A1 expression was sensitive to lenalidomide in del(5q) MDS patients. Fink concluded her talk by stating that lenalidomide provides the first example of an FDA-approved and clinically effective drug that derives its therapeutic window from specifically targeting a haploinsufficient gene.

The final presentation during the plenary session provided results from a multi-collaborative trial, the SORAML Trial (NCT00893373), conducted in Germany, presented by Christoph Röllig, MD, from Universitätsklinikum in Dresden, Germany. The trial was designed to evaluate the kinase inhibitor sorafenib as add-on to standard chemotherapy-as-backbone induction and consolidation treatment in patients with acute myeloid leukemia (AML). The primary eligibility criteria for the trial, which enrolled 276 patients from 25 centers over a period of 2.5 years, were newly diagnosed AML, aged 18 to 60 years, and suitability for intensive therapy. "Our exclusion criteria included heart disease, anaplastic leukemia, hypertension, surgery, or open wounds," said Röllig.

Röllig presented the following treatment plan:

Two cycles of induction with daunorubicin (DA) (DA 60 mg/m^2: days 3 to 5, with cytarabine 100 mg/m^2 as a continuous infusion: days 1 to 7), followed by 3 cycles of high-dose cytarabine consolidation (3 g/m^2 once a day on days 1, 3, and 5). Nonresponders received a second induction with high-dose cytarabine and mitoxantrone (HAM) (cytarabine 3 g/m^2 once a day on days 1 to 3, plus mitoxantrone 10 mg/m^2: days 3 to 5). Allogeneic stem cell transplantation was scheduled for all intermediate-risk patients in first complete remission with a sibling donor and for all high-risk patients with a matched related or unrelated donor. At study inclusion, patients were randomized to receive either sorafenib (800 mg/day) or placebo as add-on to standard treatment in a double-blinded fashion. Study medication was administered on days 10 to 19 of DA I+II or HAM, from day 8 of each consolidation until 3 days before the start of the next consolidation, and as maintenance for 12 months after the end of consolidation.

The patients were nearly evenly split between the study arm and the placebo arm, and the median cumulative dose of study medication was similar between the arms. At the end of the trial, analysis of the results found no difference in the complete remission (CR) rates between the sorafenib arm and the placebo-controlled arm, showed Röllig: CR was 59% with placebo and 60% with sorafenib (P = .764). However, he presented a significant difference in event-free survival (EFS) rates between the 2 arms: 22% versus 40% EFS for placebo and sorafenib, respectively. He pointed out that the relapse-free survival (RFS) rate was 38% in patients treated with placebo following standard treatment, while patients treated with sorafenib had a RFS of 56%. Patients in the sorafenib arm were at an increased risk for fever, infections, and bleeding events.

Röllig concluded that in younger AML patients, the addition of sorafenib to standard chemotherapy in a sequential manner is feasible and associated with antileukemic efficacy. He emphasized, however, that confirmatory trials will be necessary to establish sorafenib as a new standard therapy for AML. **EBO**

Data Show High Response Rate to Ibrutinib Combination for Patients With Hard-to-Treat MCL

Mary K. Caffrey

Results presented December 8, 2014, at the 56th Annual Meeting of the American Society of Hematology (ASH) show that 88% of patients with relapsed or refractory mantle cell lymphoma (MCL) responded to a combination of ibrutinib and rixtuxmab.

The phase 2 trail, led by Michael Wang, MD, of the University of Texas MD Anderson Cancer Center in Houston, found responses in 40 of 46 patients, with a complete response (CR) in 40%.[1] The trial also revealed an apparent marker for who will benefit most from the combination. Results found that in 34 evaluable patients with levels of less than 50% of the Ki-67 protein, the overall response rate (ORR) was 100%. Conversely, 10 patients who discontinued treatment when their MCL progressed had Ki-67 levels above 60%.[1]

Ibrutinib, being developed as Imbruvica by Pharmacyclics and Janssen Biotech, Inc, may offer an option in combination for patients whose MCL is especially difficult to treat, Wang said.[2] Previously, Wang and colleagues reported a 68% ORR in patients with relapsed/refractory MCL when ibrutinib was used as a monotherapy.[3]

"The positive outcomes seen with Imbruvica in combination with rituximab reinforce our decision to pursue its full potential as a single agent and in combination with other therapies, and underscores the potential Imbruvica may offer to patients living with hematologic malignancies," said Danelle James, MD, MS, vice president, clinical development, Pharmacyclics.[3]

LONG-TERM DATA SHOW SAFETY, DURABILITY

More than 30% of patients with relapsed or refractory MCL who were treated with ibrutinib for more than 2 years remained progression-free with no new or unexpected adverse events (AEs), according to results presented December 8, 2014, at ASH.[4] This second phase 2 trial looked at ibrutinib's safety and efficacy as a monotherapy in MCL patients who had previously been treated with rituximab combination therapy and at least 2 cycles of bortezomib. Of the 111 patients in the original study, 47% were still alive at the at the time of data cutoff.[4]

IBRUTINIB AFTER OTHER THERAPY

Wang also presented a poster with results from a phase 2, multi-center, single-arm trial (MCL2001) that investigated once-daily ibrutinib in 120 patients with relapsed/refractory MCL who previously had received a rituximab-containing treatment regimen and had progressed after at least 2 cycles of bortezomib.[5]

An independent review committee found that the ORR, which was the primary endpoint, was 63% after a median follow-up of 14.9 months, and 21% of the patients achieved a complete response. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Median DOR based on the committee's assessment was 14.9 months, and the median time to first response was 2.1 months. The median PFS was 10.5 months, with 47% of patients remaining progression-free at 1 year. The median PFS has not yet been reached. The OS rate at 18 months was 61%.[5]

The most frequently reported AEs of any grade were fatigue (43%) and diarrhea (43%). Diarrhea, when observed generally occurred early after initial treatment, but resolved quickly and was not treatment limiting. The majority of AEs were grade 1 and 2. The most common AEs ≥ grade 3 were neutropenia (21%), thrombocytopenia (13%), and pneumonia (13%). Atrial fibrillation was reported in 13 patients (11%); 6 patients (5%) experienced Grade 3 or 4 atrial fibrillation which resolved in 1 to 4 days. Five of these 6 patients had a history of atrial fibrillation.[5] **EBO**

References

1. Wang M, Hagemeister F, Westin JR, et al. Ibrutinib and rituximab are an efficacious and safe combination in relapsed mantle cell lymphoma: prelimary results from a phase 2 clinical trial. *Blood*. 2014;124(21):abstract 627.

2. Imbruvica (ibrutinib) in combination with rituximab data shows positive benefit-risk profile in hematologic malignancy [press release]. San Francisco, CA: Pharmacyclics; December 8, 2014.

3. Wang M, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369:507-516.

4. Imbruvica (ibrutinib) data demonstrates safety and durability of responses at 2-year follow-up in mantle cell lymphoma [press release]. San Francisco, CA: Pharmcyclics; December 8, 2014.

5. Wang M, Goy A, Martin P, et al. Efficacy and safety of single-agent ibrutinib in patients with mantle cell lymphoma who progressed after bortezomib therapy. *Blood*. 2014;124(21):abstract 4471.

Improved Cancer Care Through Innovation

Surabhi Dangi-Garimella, PhD

Cancer care has influenced every aspect of our society. The discovery of new targeted therapies, the development of better drug delivery systems, facilitating patient access to therapy, and innovative approaches to hold down treatment costs are just a few of the strategies that can contribute to improved patient care, especially from a drug developer's perspective. However, innovation can prove challenging for the pharmaceutical industry, especially with respect to reimbursement.

Revolutionizing patient care, however, needs much more, as was revealed during conversations with payer representatives from leading managed care enterprises during the Oncology Stakeholders Summit: Insights discussion organized by *The American Journal of Managed Care* in the fall of 2014. Participants included Irwin W. Tischler, DO, national medical director, oncology, for Cigna, and Bryan Loy, MD, physician lead–cancer, Humana. Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care at NewYork-Presbyterian Hospital, interviewed the experts.

Salgo began by asking the experts what were the most influential innovations in oncology over the previous decade. Tischler considered personalized treatment and molecular diagnostics to individualize treatment as most important; he regarded these developments as a means to reduce side effects and provide care tailored to treat a specific genetic abnormality, and only sees the role of personalized therapy evolving and getting even more specific over time. Loy recognized the increasing openness among various groups about their cancer experiences. He thinks we have come a long way, with all stakeholders involved—patients, payers, providers, and policy experts—grabbing on to a common platform to discuss cost-effective ways of utilizing technology to improve patient care. "We wouldn't have heard that 10 to 12 years ago," he said.

Loy acknowledged that molecular testing has had a huge impact on cancer treatment options. He sees even more opportunity in gathering stakeholders to make best of this tremendous scientific achievement. Citing Kentucky, his home state, as an example, Loy said that contextualizing risk is difficult for some patients. With the biomarker tests, however, results and disease risk can be assigned a definitive value to help bring things into perspective for the patient. The dialogue also highlights shared accountability among all involved.

Rep Fred Upton (R-Michigan) and Rep Diana DeGette (D-Colorado) have launched the 21st Century Cures initiative to "bridge the gap between the science of cures and the way the therapies are regulated." A dialogue has already begun between the committee and various stakeholders from the healthcare world.[1] "Do you see this initiative impacting some of the regulatory barriers that currently impact the industry?" asked Salgo. Tischler said he expects this initiative, coupled with the influence of the current digital revolution, to improve patient access to novel therapies. He said the initiative is looking for suggestions and solutions to move the process without the oversight and regulation that have been a barrier to drug development thus far. Loy, too, acknowledged that the initiative is a healthy first step to hasten

(continued on page **SP30**)

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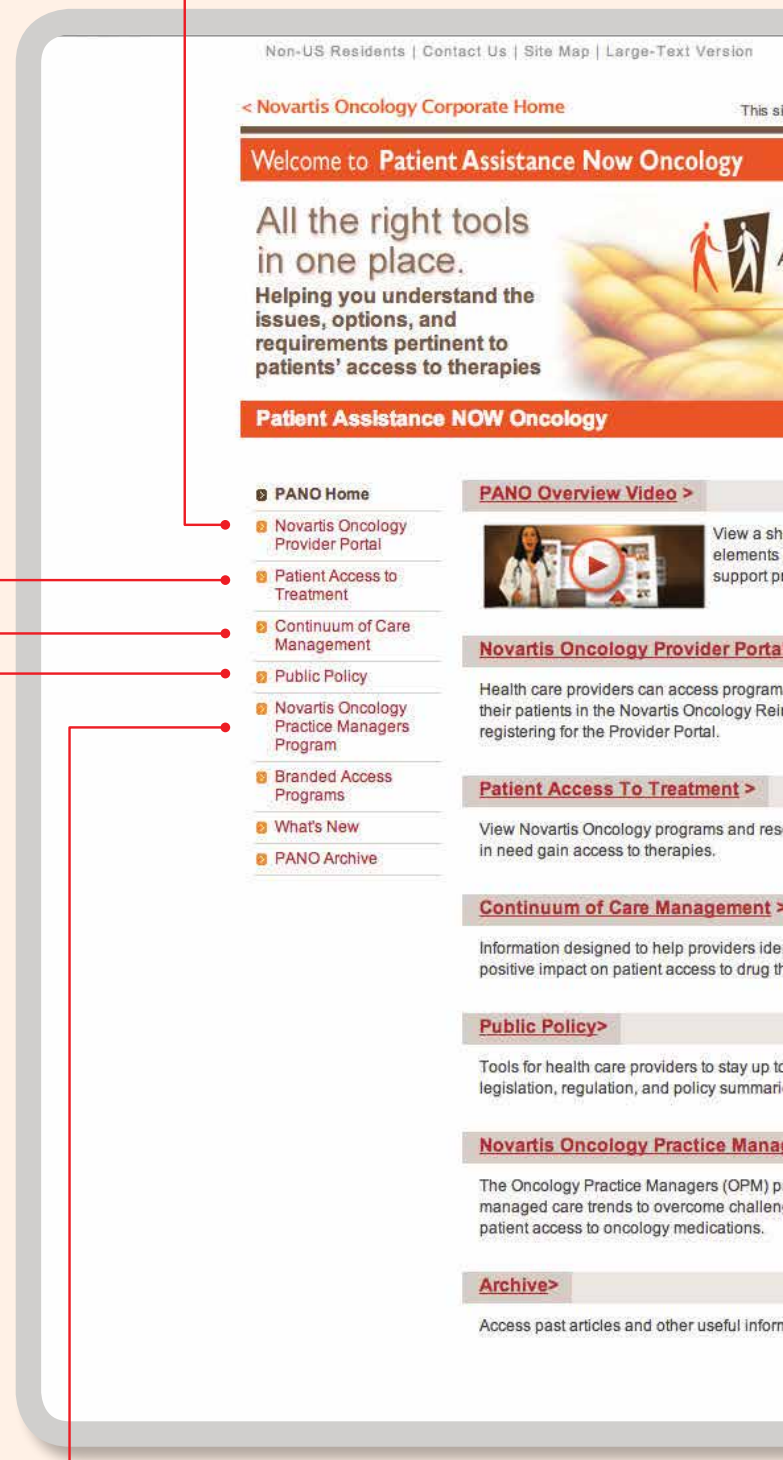

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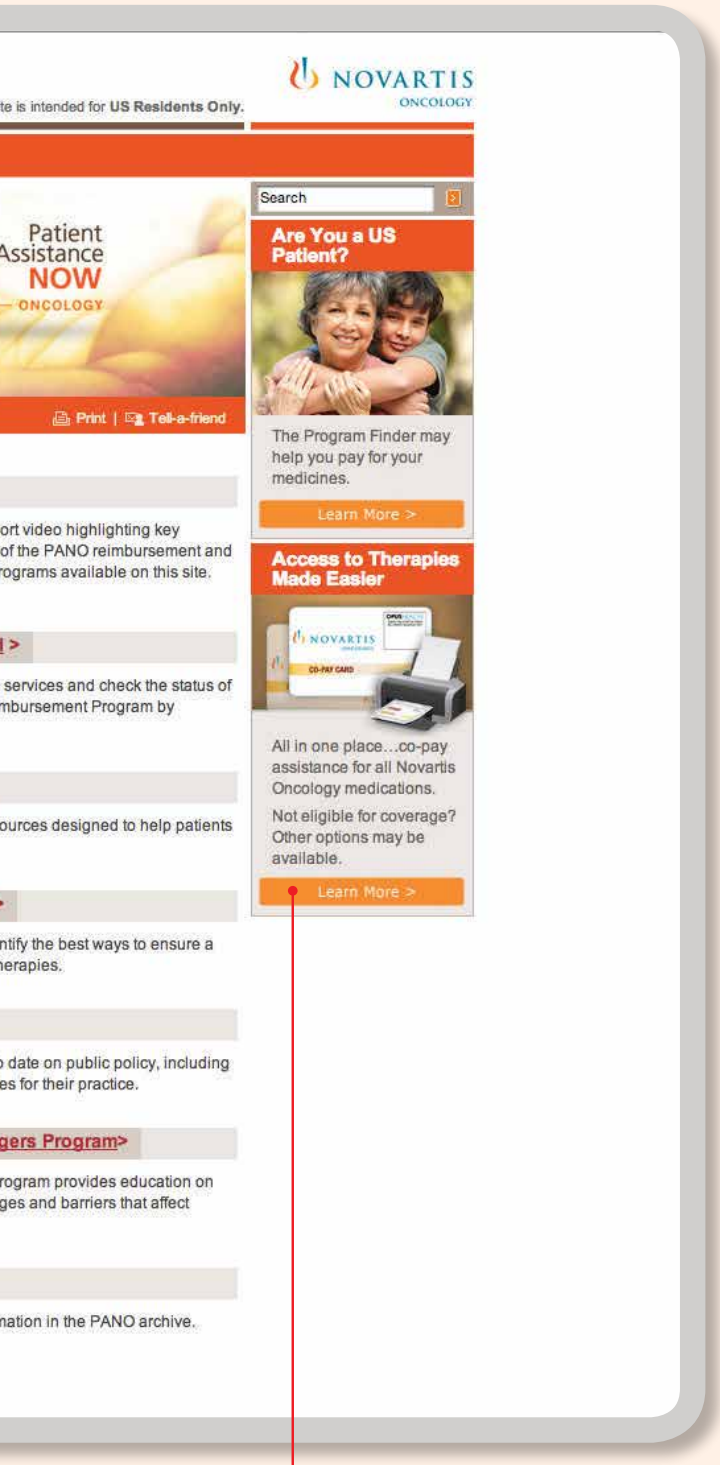

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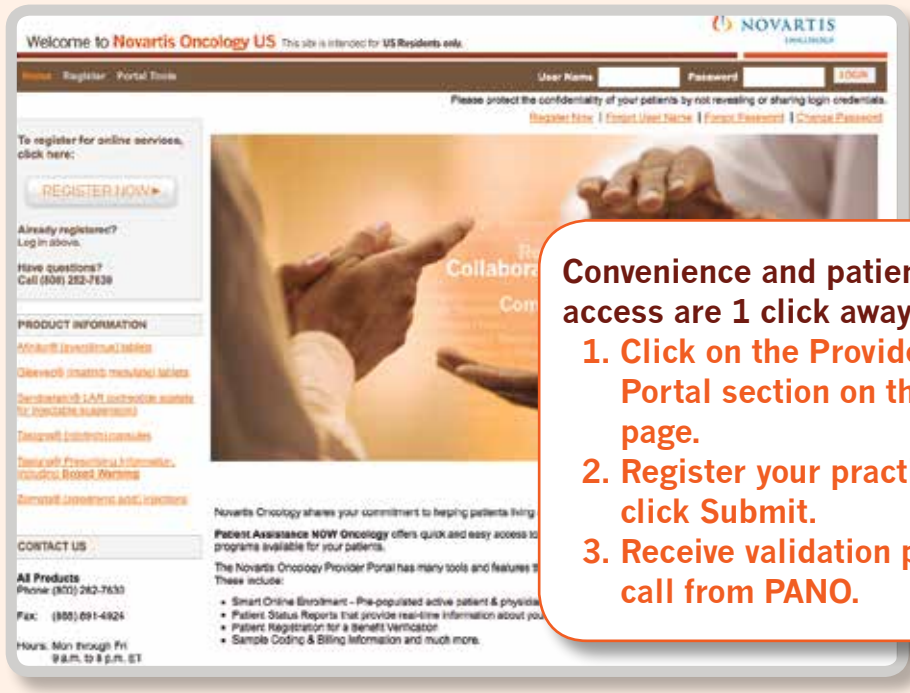

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the drug development process so patients gain access to novel treatment options. Whether and how they exploit available treatments will vary, he said.

Both Loy and Tischler agreed that the pharmaceutical industry faces tremendous risks during product development, but Tischler believes the initiative is working to overcome some of these barriers. "If we can adopt something along these lines that this bill is purporting to do, it may lower some of the costs and enable us to use some of the technologies that are available. And I think that if there is still a return on their investment dollar and their research dollars, they won't be as adverse to it," he said. Loy also believes in the potential of an adaptive clinical trial design, especially in the search for breakthrough therapies. According to Loy, the existence of guidelines alone would bring tremendous clarity to the drug development process, even if it does not have a direct influence on the pace of innovation.

PERSONALIZED MEDICINE AND THE CHALLENGE OF PHARMACOGENOMICS

While personalized medicine presents a tremendous opportunity to improve treatment outcomes, the challenge lies in its high cost, analyzing the vast amount of data generated from the genomic tools, and making sense out of those tools. Tischler stated that pharmacogenomics applications are in preliminary stages and currently do not have any clinical utility, but that payers end up covering their expenses anyway. Loy agreed, saying that payers need to be convinced about the value of spending money on personalized treatment options while distinguishing between the clinical utility of a genomic test versus patient eligibility for a future trial.

An important consideration that needs improvement is the lack of communication between all those involved in personalized testing, said Loy. This results in tests being conducted but results not being shared to allow for more-informed treatment decisions. This is especially important when decisions to not treat a patient are made based on a test. "You really need to make sure that if you are deciding not to treat, that you're not living with regret later on because of your unknown risk tolerance and unknown understanding of probability," Loy said.

MEDICARE REIMBURSEMENT POLICIES AND PHARMACEUTICAL INNOVATION

Both Loy and Tischler pointed to several issues associated with Medicare, especially sequestration, which primarily harmed reimbursement rates for oncologists. And patients who stand to gain from the treatment have high cost sharing or high deductibles, which, in cancer care, has resulted in bankruptcies, said Loy. To help ease difficult decisions of choosing between treatment and affording a normal life, Loy's solution is to hold multistakeholder conversations now, rather than later, and to center them around cost issues. He thinks these decisions must be made early on in the treatment process to help patients "fight their battle by making reasonable choices, rather than wait until a catastrophic situation arises."

One of the solutions that Tischler suggested was having 1 deductible and 1 co-payment that would cover the entire treatment, rather than individual co-pays per visit or per prescription. "We're talking about it with some employer groups, with our national teams to see if by one deductible, one co-pay, it covers their entire treatment," he said. **EBO**

Payers Look to CER for Improved Healthcare Decisions

Surabhi Dangi-Garimella, PhD

With the growing burden of the cost of cancer therapy, for both payers and society as a whole, cost-effectiveness discussions are on the rise among all stakeholders—payers, providers, and patients. Organizations like the American Society of Clinical Oncology have joined the discussion and are developing a framework that could help physicians and patients reach treatment decisions together. While the healthcare system in the United States is struggling to balance access to care with the cost of that care, comparative effectiveness research (CER) could lead to better-informed healthcare decisions.

The value of CER was discussed by a group of payer representatives during the Peer Exchange convened by *The American Journal of Managed Care* in September 2014, Oncology Stakeholder Summit: Evidence-Based Decisions to Improve Quality and Regulate Costs. Participants included **John L. Fox, MD, MHA,** senior medical director and associate vice president of Medical Affairs at Priority Health; **Ira M. Klein, MD, MBA, FACP,** national medical director, Clinical Thought Leadership, Office of the Chief Medical Officer, Aetna Inc; **Michael Kolodziej, MD,** national medical director for Oncology Strategies, Aetna Inc; **Bryan Loy, MD,** physician lead–Cancer, Humana; and **Irwin W. Tischler, DO,** national medical director, Oncology, Cigna. The session was moderated by **Peter Salgo, MD,** professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care at NewYork-Presbyterian Hospital.

Michael Kolodziej, MD

Kolodziej began the discussion with a comparison between the European healthcare system and that of the United States. While CER guides policy decisions in Europe, especially by Britain's National Institute for Health and Clinical Excellence (NICE), it has not found widespread acceptance in the United States, with critics equating CER with rationing of healthcare to save costs. The Patient-Centered Outcomes Research Institute (PCORI), a product of the Affordable Care Act, was considered by many as a solution to tackling CER, but was prevented from considering the cost of care in its research, Kolodziej said. "So I think that this is a fertile soil. I don't think the payers are going to do it, but I think they're dying to use it," he added.

He went on to cite a project that he is involved in, a project to identify the optimal drug sequence in breast cancer and renal cell cancer. Although this is a very challenging task, Kolodziej said that pointing out the worst sequence would be equally effective. Loy added that while CER has been used by pharmacies and pharmacy benefit managers for some time (as step therapy), it could have tremendous utility in the healthcare delivery model.

When Salgo asked the payers about CER in a clinical trial setting, several of them agreed that it would be a huge advantage to trials. CER works as the phase 4 of a clinical trial for the FDA, said Klein, "a post trial real-world analysis" that would provide a much clearer picture of a drug's performance than an actual clinical trial with its highly controlled environment would.

Irwin W. Tischler, DO

When the discussion moved toward the importance of including quality-adjusted life-years (QALYs) in CER, Kolodziej emphasized the role of patient-reported outcomes in the QALY discussion. The real question, the panel agreed, is whether decisions should be made on a case-per-case basis after evaluating a patient's status and respecting patient opinion, or whether a general policy should be crafted after establishing cost-effectiveness of a therapy. As the discussion circled back to patient age and cost of care, Tischler suggested that in the case of an older patient, the treating physician should be obligated to discuss the cost of therapy with the patient and the family. "Like I used to say to my patients, I could add a lot of years to your life or some years to your life, but I'm not going to add a whole lot of life to your years, and what price are you willing to pay for that? I think that's where the discussion should go," he added. While these extremely important discussions on cost of care are in their preliminary stages, Tischler said he could foresee them being a part of mainstream healthcare decisions in the near future.

Fox concurred, and emphasized the importance of communicating available options to the patients and family members, stating that the question of "rationing" care may not arise if the patient is well aware of the different ways to achieve the desired outcome. "In our experience in working with providers to do advanced care planning around patients who have terminal diseases, a lot of patients, once they fully understand the options, say, 'You know, I don't want more treatment. I want to be kept comfortable,'" added Fox.

While CMS is prohibited from considering CER to approve coverage for a particular treatment, Fox said that payers have a straightforward method of accounting for a very expensive drug: increased premium or co-pay. Klein added that these increases in patient cost-sharing lead to an informal rationing, with a steep decrease in adherence. "We're creating a multi-tiered system in which rationing occurs by the financial burdens we put on people, and we put those burdens on people actuarially because we have decided not to fix the problem on the front end," said Klein. **EBO**

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Bigger Regulatory Challenges in Diagnostics Than in Therapeutics, Industry Expert Says

Mary K. Caffrey

For makers of cancer therapies, the regulatory environment in Europe is likely to become more like that of the United States, and the FDA may extend its reach to areas such as next-generation sequencing.

That's what an industry expert told attendees gathered at a joint symposium of the American Society of Hematology (ASH) and the European Hematology Association, during the 56th Annual Meeting of ASH held at the Moscone Center in San Francisco.

David R. Parkinson, MD, of New Enterprise Associates, Inc, in Menlo Park, California, offered an industry perspective on the current regulatory climate, while Ann T. Farrell, MD, spoke on behalf of the FDA. Both Farrell and Parkinson spent time discussing the growing challenges in the molecular diagnostics realm, an area where the FDA seeks increased oversight to ensure reliability.

As reported throughout 2014 by *Evidence-Based Oncology*,[1,2] the diagnostics industry has been rocked by uncertainty over reimbursement, which has resulted in lawsuits and the loss of some small companies. Plus, the FDA moved on July 31, 2014, to extend oversight to an estimated 11,000 laboratory developed tests, including highly complex tests to direct cancer treatment and other chronic illnesses.[3]

While this move was seen by some as essential to ensure patient safety, it is viewed by others as overregulation that will stifle creativity in genomic medicine. Others in the industry are taking a pragmatic view: if regulation must come, perhaps the FDA's blessing will also mean the path to payer reimbursement will become clear. Dueling viewpoints were featured in the January 5, 2015, issue of *JAMA Oncology*, a publication of the *Journal of the American Medical Association*.[4,5] As *Evidence-Based Oncology* went to press, the FDA was holding a 2-day workshop, "Framework for Regulatory Oversight for Laboratory Developed Tests."[6]

During the ASH session, Parkinson explained that payers began demanding evidence of clinical utility relatively recently, from an industry with "no tradition" of providing such studies. Most observers date the shift to around 2011, and say it emerged suddenly and snowballed, to the shock of the industry. Regulation of diagnostics industry, meanwhile, lacks the maturity seen on the therapeutic side, Parkinson said.

And yet the need to match the right drugs to the right patients—and the increased focus on smaller groups of patients and therapeutic targets—makes molecular diagnostic testing increasingly important, which demands more regulatory stability and policy solutions, he said.

Fifteen years ago, if one had suggested widespread investment by pharmaceutical companies in orphan disease, "You would have been laughed out of the room," Parkinson said. But over time, the combination of incentives created by 1983 legislation and poor returns on other investments by the drugmakers have caused the industry to look to smaller groups of patients for whom the return on investment may not be huge, but at least more certain. Collaborations with academia and more unique financial arrangements with philanthropy to manage risk have changed the playing field.

"If the field is to move forward, there needs to be investment," he said. Without it, "treatment will not advance."

Before Parkinson spoke, Farrell discussed the factors that go into FDA decision making: essentially, regulators balance known benefits against known risks. The EMA has "exceptional circumstance," and the FDA now has an "accelerated approval" process for therapies to treat life-threatening illnesses that are superior to available treatments. The FDA's increased flexibility in the cancer area, in particular, has been praised. Post-marketing studies are typically needed. When it comes to orphan diseases, Farrell said the FDA aims for regular approval because the agency realizes how difficult it is to do a clinical trial in the first place.

Despite the increased flexibility, the drug approval process in the United States is viewed worldwide as the most expensive and highly uncertain. Parkinson concluded the session with a call for Congress to act to give regulators and CMS new tools, or drug costs will continue to increase.

"All regulatory agencies are data driven," Farrell said. The data provided by drug makers must inform product labeling to ensure safety and efficacy "whether it's a drug, a biologic, or a device."

With an accelerated approval, the FDA wants to see evidence in the published literature, which can be based on a surrogate endpoint. The FDA will also likely ask to see additional studies after approval is granted.

The agency defines clinical benefit not only as improvement in survival, Farrell said, but in "how a patient feels, and how a patient functions."

In the diagnostic area, Farrell said there are 4 issues where the FDA envisions oversight in the development of companion diagnostic devices:

- the identification of patients who are likely to benefit from a therapy
- the identification of patients who are likely to be adversely affected by therapy
- monitoring responses to treatment with therapy
- indications and approval

Some companion diagnostics were developed in tandem with therapies, but Farrell said that is not always possible, and FDA developed protocols that recognized it does not always make sense to withhold therapy just because the diagnostic is not yet available.

When ponatinib appeared for chronic myeloid leukemia, for example, the FDA looked at prior approvals for imatinib, nilotinib, and dasatinib for guidance, Farrell said. "We decided to approve it without reference to the test," she said, but, "We took our post marketing tests very seriously." **EBO**

References

1. Caffrey MK. When science outpaces the payers: reimbursement in molecular diagnostics. *Am J Manag Care.* 2014;20(SP7):SP234-SP236.

2. Caffrey MK. Studies see value of prostate cancer diagnostic test, but will CMS pay for it? *Am J Manag Care.* 2014;20(SP11):SP323-SP327.

3. Caffrey MK. FDA moves to regulate thousands of regulatory tests. *Am J Manag Care.* 2014;20(SP11):SP338.

4. Sharfstein J. FDA regulation of laboratory-developed diagnostic tests: protect the public, advance the science [published online January 5, 2015]. *JAMA Oncology*. doi:10.1001/jama.2014.18135

5. Evans JP, Watson MS. Genetic testing and FDA regulation: overregulation threatens the emergence of genomic medicine [published online January 5, 2015]. *JAMA Oncology*. doi:10.1001/jama.2014.18145.

6. Public workshop: framework for regulatory oversight of laboratory developed tests (LDTs), January 8-9, 2015. FDA website. http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm423537.htm. Accessed January 8, 2015.

GRANIX™ (TBO-FILGRASTIM) Injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
GRANIX™ (tbo-filgrastim) Injection, for subcutaneous use

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRANIX is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

6 ADVERSE REACTIONS

The following potential serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [*see Warnings and Precautions (5.1)*]
- Acute Respiratory Distress Syndrome [*see Warnings and Precautions (5.2)*]
- Serious Allergic Reactions [*see Warnings and Precautions (5.3)*]
- Use in Patients with Sickle Cell Disease [*see Warnings and Precautions (5.4)*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.5)*]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

6.1 Clinical Trials Experience

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

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^6/L after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100,000 x 10^6/L) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of GRANIX in pregnant women. In an embryofetal developmental study, treatment of pregnant rabbits with tbo-filgrastim resulted in adverse embryofetal findings, including increased spontaneous abortion and fetal malformations at a maternally toxic dose. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In the embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure ($AUC_{0\text{-}24}$) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

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

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

Manufactured by:
Sicor Biotech UAB
Vilnius, Lithuania
U.S. License No. 1803

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Product of Israel
GRX-40188 January 2014

This brief summary is based on TBO-003 GRANIX full Prescribing Information.

GRANIX™
(TBO-FILGRASTIM)
Injection

Take a bite out of G-CSF acquisition costs*

GRANIX™ is another option in short-acting G-CSF therapy

GRANIX™ is an option for hospitals and payers to consider when determining health system budgets

- **FDA approved through the rigorous BLA† process**
- **Teva's short-acting G-CSF was first introduced in Europe in 2008 and is available in 42 countries‡[1]**
- **GRANIX J Code: J 1446-Injection, tbo-filgrastim, 5 micrograms, effective January 1, 2014**

†Biologics License Application.

‡As of February 2014.

*Based on wholesale acquisition cost (WAC) of all short-acting G-CSF products as of November 11, 2013. WAC represents published catalogue or list prices and may not represent actual transactional prices. Please contact your supplier for actual prices.

Indication

- GRANIX is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

- **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
- **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

Reference: 1. Data on file. Teva Pharmaceuticals: Filgrastim MA Approvals Worldwide. February 2014.

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