SPECIAL ISSUE: ASH MEETING RECAP

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Evidence-Based ONCOLOGY™

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HIGHLIGHTS FROM THE MEETING

- PROGRESS IN CAR T-CELL THERAPY: UPDATES ON THE JULIET AND ZUMA-1 TRIALS, **SP6**.
- PROMISING RESULTS FOR SINGLE-AGENT IBRUTINIB IN MCL AND CLL, **SP8**.
- CLONAL EXPANSION AND AGING FUEL THE DEVELOPMENT OF NEOPLASMS, **SP10**.
- A NEW TREATMENT PARADIGM IN ADVANCED HODGKIN LYMPHOMA? THE ECHELON-1 STUDY, **SP18**.
- BALANCING HOSPICE UTILIZATION WITH THE NEED FOR TRANSFUSION IN LEUKEMIA, **SP19**.
- BIOSIMILARS UPDATE, **SP24-SP27**.

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Effective January 1, 2018, the following code can be used for administrative and billing purposes specific to LARTRUVO™ (olaratumab):

J9285, INJECTION, OLARATUMAB, 10 MG

Strength	NDC
500 mg/50 mL	**0**0002-8926-01
190 mg/19 mL	**0**0002-7190-01

*Note that the product's NDC code has been "zero–filled" to ensure creation of an 11-digit code that meets HIPAA standards. The zero-fill location is indicated in bold.
NDC=National Drug Code; HIPAA=Health Insurance Portability and Accountability Act.

Vials are not actual size.

How Supplied	LARTRUVO is supplied as 190 mg/19 mL and 500 mg/50 mL (10 mg/mL), single-dose vials.

INDICATION

LARTRUVO is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

IMPORTANT SAFETY INFORMATION FOR LARTRUVO

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

- Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.3%) of 485 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest. Infusion-related reactions required permanent discontinuation in 2.3% of patients and interruption of infusion in 10% of patients. All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO; 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N = 485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication. Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR.

Embryo-Fetal Toxicity

- Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

MOST COMMON ADVERSE REACTIONS/LAB ABNORMALITIES

- The most commonly reported adverse reactions (all grades; grade 3-4) occurring in ≥20% of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were nausea (73% vs 52%; 2% vs 3%), fatigue (69% vs 69%; 9% vs 3%), musculoskeletal pain (64% vs 25%; 8% vs 2%), mucositis (53% vs 35%; 3% vs 5%), alopecia (52% vs 40%; 0% vs 0%), vomiting (45% vs 19%; 0% vs 0%), diarrhea (34% vs 23%; 3% vs 0%) decreased appetite (31% vs 20%; 2% vs 0%), abdominal pain (23% vs 14%; 3% vs 0%), neuropathy (22% vs 11%; 0% vs 0%), and headache (20% vs 9%; 0% vs 0%).
- The most common laboratory abnormalities (all grades; grade 3-4) occurring in ≥20% of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were lymphopenia (77% vs 73%; 44% vs 37%), neutropenia (65% vs 63%; 48% vs 38%) and thrombocytopenia (63% vs 44%; 6% vs 11%), hyperglycemia (52% vs 28%; 2% vs 3%), elevated aPTT (33% vs 13%; 5% vs 0%), hypokalemia (21% vs 15%; 8% vs 3%), and hypophosphatemia (21% vs 7%; 5% vs 3%).

USE IN SPECIFIC POPULATIONS

- Lactation: Because of the potential risk for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LARTRUVO and for at least 3 months following the last dose.

OR HCP ISI 19OCT2016

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

Lilly

Lartruvo™
(OLARATUMAB)
Injection 10 mg/mL

LARTRUVO™ (olaratumab) injection
BRIEF SUMMARY: For complete safety, please consult the full Prescribing Information.

INDICATIONS AND USAGE

LARTRUVO is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.3%) of 485 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest. Infusion-related reactions required permanent discontinuation in 2.3% of patients and interruption of infusion in 10% of patients. All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO; 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N = 485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication. Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR.

Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the Warnings and Precautions section reflect exposure to LARTRUVO in 485 patients from three randomized, open-label, active-controlled clinical trials, which enrolled 256 patients with various tumors who received LARTRUVO in combination with chemotherapy (191 patients) or LARTRUVO as a single agent (65 patients); four open-label single-arm trials which enrolled 96 patients with various tumors who received LARTRUVO as a single agent at doses of 10 to 20 mg/kg; and two trials, including Trial 1, which enrolled 133 patients with soft tissue sarcoma who received LARTRUVO at doses of 15 to 20 mg/kg in combination with doxorubicin (103 patients) or LARTRUVO as a single agent (30 patients). Among the 485 patients, 25% were exposed to LARTRUVO for ≥6 months and 6% were exposed for ≥12 months. The data described below reflect exposure to LARTRUVO in 64 patients with metastatic soft tissue sarcoma enrolled in Trial 1, a multicenter, randomized (1:1), open-label, active-controlled trial comparing LARTRUVO plus doxorubicin with doxorubicin as a single agent. LARTRUVO was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity [see Clinical Studies (14)]. All patients received doxorubicin 75 mg/m^2 as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and received dexrazoxane, prior to doxorubicin in cycles 5 to 8. In Trial 1, no patients had received a prior anthracycline-containingregimen. The trial excluded patients with an ECOG performance status >2; left ventricular ejection fraction <50%; or unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months. Baseline demographics and disease characteristics were: median age 58 years (range 22 to 86); 45% male; 87% White, 8% Black, 3% Asian, 2% Other; 57% ECOG PS 0, 39% ECOG PS 1, and 5% ECOG PS 2. The median duration of exposure to LARTRUVO was 6 months (range: 21 days to 29.4 months) with 36 (56%) patients receiving LARTRUVO for ≥6 months and 10 (16%) patients receiving LARTRUVO for ≥12 months. The median cumulative doxorubicin dose was 488 mg/m^2 in the LARTRUVO plus doxorubicin arm and 300 mg/m^2 in the doxorubicin arm.In Trial 1, adverse reactions resulting in permanent discontinuation of LARTRUVO occurred in 8% (5/64) of patients. The most common adverse reaction leading to LARTRUVO discontinuation was infusion-related reaction (3%). Dose reductions of LARTRUVO for adverse reactions occurred in 25% (16/64) of patients; the most common adverse reaction leading to dose reduction was Grade 3 or 4 neutropenia (20%). Dose delays of LARTRUVO for adverse reactions occurred in 52% (33/64) of patients; the most common adverse reactions resulting in dose delays were neutropenia (33%), thrombocytopenia (8%), and anemia (5%). Table 1 summarizes adverse reactions that occurred in at least 10% of patients receiving LARTRUVO in the randomized portion of the study. The most common adverse reactions reported in at least 20% of patients receiving LARTRUVO plus doxorubicin were nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache.

Table 1: Adverse Reactions Occurring in ≥10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)

Adverse Reactions	LARTRUVO plus Doxorubicin N=64		Doxorubicin N=65	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Nausea	73	2	52	3
Mucositis	53	3	35	5
Vomiting	45	0	19	0
Diarrhea	34	3	23	0
Abdominal Pain[a]	23	3	14	0
General Disorders and Administrative Site Conditions				
Fatigue[b]	69	9	69	3
Infusion-Related Reactions	13	3	3	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[c]	64	8	25	2
Skin and Subcutaneous Tissue Disorders				
Alopecia	52	0	40	0
Metabolic and Nutritional Disorders				
Decreased Appetite	31	2	20	0
Nervous System Disorders				
Neuropathy	22	0	11	0
Headache	20	0	9	0
Psychiatric Disorder				
Anxiety	11	0	3	0
Eye Disorder				
Dry Eyes	11	0	3	0

[a] Abdominal pain includes: abdominal pain, lower abdominal pain, and upper abdominal pain.
[b] Fatigue includes: asthenia and fatigue.
[c] Musculoskeletal pain includes: arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity.

LARTRUVO™ (olaratumab) injection OR HCP BS 21OCT2016

In Trial 1, the most common laboratory abnormalities (≥20%) were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia as shown in Table 2.

Table 2: Laboratory Abnormalities Worsening from Baseline in >10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and Occurring at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)

Laboratory Abnormality	LARTRUVO plus Doxorubicin[a]		Doxorubicin[a]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry				
Hyperglycemia	52	2	28	3
Increased aPTT[b]	33	5	13	0
Hypokalemia	21	8	15	3
Hypophosphatemia	21	5	7	3
Increased Alkaline Phosphatase	16	0	7	0
Hypomagnesemia	16	0	8	0
Hematology				
Lymphopenia	77	44	73	37
Neutropenia	65	48	63	38
Thrombocytopenia	63	6	44	11

[a] The incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: LARTRUVO plus doxorubicin arm (range 60 to 63 patients) and doxorubicin arm (range 39 to 62 patients).
[b] aPTT = activated partial thromboplastin time

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, 13/370 (3.5%) of evaluable LARTRUVO-treated patients tested positive for treatment-emergent anti-olaratumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in all patients who tested positive for treatment-emergent anti-olaratumab antibodies. The effects of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed due to the limited number of patients with treatment-emergent anti-olaratumab antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to LARTRUVO with the incidences of antibodies to other products may be misleading.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm. There are no available data on LARTRUVO use in pregnant women. No animal studies using olaratumab have been conducted to evaluate its effect on female reproduction and embryo-fetal development. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis at exposures less than the exposure at the maximum recommended human dose caused malformations and skeletal variations *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
No animal studies have been conducted using olaratumab to evaluate the effect of blocking PDGFR-α signaling on reproduction and embryo-fetal development. In PDGFR-α knockout mice, disruption of PDGFR-αα signaling resulted in embryo-fetal lethality and teratogenicity, including cleft face and spina bifida. Intravenous administration of an anti-murine PDGFR-α antibody once every 3 days to pregnant mice during organogenesis at 50 and 150 mg/kg resulted in increased malformations (abnormal eyelid development) and skeletal variations (additional ossification sites in the frontal/parietal skull). Increased post-implantation loss occurred at a dose of 5 mg/kg. The effects on fetal development in mice administered this antibody occurred at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg LARTRUVO.

Lactation
Risk Summary
There are no data on the presence of olaratumab in human milk, or its effects on the breastfed infant or on milk production. Because of the potential risk for serious adverse reactions in breastfeeding infants from olaratumab, advise women not to breastfeed during treatment with LARTRUVO and for 3 months following the last dose.

Females and Males of Reproductive Potential
Contraception
Females
Based on its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

Infertility
Males
Based on animal models, LARTRUVO may impair male fertility.

Pediatric Use
The safety and effectiveness of LARTRUVO in pediatric patients have not been established.

Geriatric Use
Clinical studies of LARTRUVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

PATIENT COUNSELING INFORMATION
Infusion-Related Reactions
Advise patients to report signs and symptoms of infusion reactions.
Embryo-Fetal Toxicity
Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential of the potential risk to the fetus, to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy.
Lactation
Advise patients not to breastfeed during treatment with LARTRUVO and for 3 months after the last dose.

Additional information can be found at www.LARTRUVO.com/hcp.

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

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SPECIAL ISSUE / ASH MEETING RECAP
JANUARY 2018
VOLUME 24, ISSUE 1

CAR T PROGRESS

SP6

Global Submissions for Kymriah, 42% Ongoing Response With Yescarta in ZUMA-1 Patients

INSIDE THE ISSUE

FROM THE CHAIRMAN

SP5 At ASH, Another Year of Wondrous Science and Worry for Payers

CLINICAL

SP6 CAR T Progress: Global Submissions for Kymriah, 42% Ongoing Response With Yescarta in ZUMA-1Patients

SP8 Single-Agent Ibrutinib Promising in MCL and CLL, Improves Patient Well-Being

SP10 Clonal Expansion and Aging Fuel the Development of Neoplasms, Say Experts at ASH

SP11 Treatment-Free Remission and Preventing Cardiotoxicity: The Future of CML Care

SP17 Ibrutinib Is More Effective Than Stem-Cell Transplant in Patients With Form of Chronic Leukemia

SP18 New Treatment Paradigm Supersedes ABVD in Advanced Hodgkin Lymphoma: The ECHELON-1 Study

QUALITY OF LIFE

SP19 Balancing Hospice Utilization With the Need for Transfusion in Leukemia

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FROM THE CHAIRMAN

At ASH, Another Year of Wondrous Science and Worry for Payers

MEDICINE'S GREATEST MARVELS—and toughest questions—came together again this year at the 59th Annual Meeting of the American Society of Hematology (ASH), which we cover in this special issue of *Evidence-Based Oncology*™ (*EBO*™). For a second year, the possibilities of chimeric antigen receptor (CAR) T-cell treatments took center stage, as researchers from the University of Pennsylvania followed up the breakthrough that led to the August approval of tisagenlecleucel (Kymriah), the first treatment of its kind.

HENNESSY

Creating hope for patients with previously incurable leukemia or lymphoma is what propels our brightest minds, who can now take a patient's own cells and engineer them to attach and to kill cancer cells. But this process is complex and the cost is high. The announced cost of tisagenlecleucel, $475,000, is the subject of 2 studies covered in this issue, which address the value of this treatment. The first approved use of tisagenlecleucel, for certain patients with pediatric acute lymphoblastic leukemia (ALL), affected a very small population—the FDA said only about 3100 patients under age 20 are diagnosed with ALL each year, and this treatment would not be used in most of them. But the next approved CAR T-cell treatment affected a larger group of patients, and as approvals continue, the numbers of eligible patients will multiply. As this happens, who will gain access? Will the price come down? There are multiple reports that Novartis and CMS have worked on an outcomes-based payment agreement, so that Medicaid only pays for the treatment when it works. But other reports say early billing has been difficult.

Results for other therapies and combinations reported at ASH included promising findings for single-agent ibrutinib in relapsed/refractory mantle cell lymphoma and in chronic lymphocytic leukemia, and a new treatment combination in advanced Hodgkin lymphoma. Fortunately, ASH is also bringing news of how payers and patients are exerting more control over costs and care as well as studies about the best outcome: *stopping* treatment, which could be a possibility for patients with chronic myelogenous leukemia. As cancer treatment extends life, science measures not just its length but also its quality, and in ways that ensure the patient voice is heard.

As always, we thank you for reading this special issue of *EBO*™ and we welcome your feedback. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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CONTENTS (CONTINUED)

JANUARY 2018, VOLUME 24, ISSUE 1

COST OF CARE
SP23
Kymriah More Cost-Effective in Pediatric Patients With Acute Lymphoblastic Lymphoma

SP20 Using Time Spent at Home to Measure End-of-Life Care Quality

SP21 Patients With AL Amyloidosis From Lower Socioeconomic Status Report Lower Quality of Life

SP21 The Effects of Myeloproliferative Neoplasm Symptoms on Quality of Life

COST OF CARE

SP22 Significant Economic Burden Associated With Various AML Treatment Episodes

SP22 Financial Incentives May Lead to Overuse of Rituximab Maintenance

SP23 Kymriah More Cost-Effective in Pediatric Patients With Acute Lymphoblastic Lymphoma

BIOSIMILARS UPDATE

SP24 New Data Support Using Tbo-Filgrastim in Pediatric Patients

SP25 Study Results Show Low Incidence of Immunogenicity With Tbo-Filgrastim

SP26 2 Studies Highlight Biosimilar G-CSFs

SP27 Presenters Share New Data on Rituximab Biosimilars Approved in European Union, Argentina

AJMC®TV

AJMC®TV INTERVIEWS

SP28 Dr Stephen Schuster Outlines CAR T Results Seen in Leukemia, Lymphoma, and Myeloma

Dr Julie Wolfson Highlights Different Outcomes in AYAs With ALL Compared With Children

Dr Joshua Richter Discusses the Patient Financial Burden of New Treatments and Cures

SP29 Dr Thomas LeBlanc: Patients With Blood Cancers Less Likely to Use Hospice Care

Dr Nina Shah on the Benefits of Outpatient HSCT When Possible

Dr Derek Raghavan Outlines Challenges to Implementing Evidence-Based Guidelines

Dr Kerry Rogers: Ibrutinib's Impact on Vaccine Response

CLINICAL

CAR T Progress: Global Submissions for Kymriah, 42% Ongoing Response With Yescarta in ZUMA-1 Patients

Surabhi Dangi-Garimella, PhD

A MUCH-ANTICIPATED SESSION On the second day of the 59th Annual Meeting and Exposition of the American Society of Hematology (ASH) in Atlanta, Georgia, provided long-term updates on trials evaluating 2 chimeric antigen receptor (CAR) T-cell treatments: tisagenlecleucel, or CTL019 (Kymriah), for the treatment of adult relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), and axicabtagene ciloleucel (Yescarta), which was evaluated in patients with refractory aggressive non-Hodgkin lymphoma (NHL).

Tisagenlecleucel was the first CAR T-cell treatment to be approved in certain pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia. Results from the single-arm, open-label, multicenter, global, pivotal phase 2 JULIET trial of CTL019 in adults with r/r DLBCL were presented by Stephen Schuster, MD, professor, Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania.[1] Conducted in 27 study centers located in 10 countries around the world, the CAR T cells were manufactured in the United States and Germany.

The primary objective was met at the interim analysis, with the best overall response rate (ORR) of 59%, Schuster reminded the audience. His presentation provided results from the primary analysis of JULIET data, with the primary endpoint defined as best ORR (complete response [CR] + partial response [PR]) per independent review committee.

Eligibility criteria for JULIET included age 18 or older with r/r DLBCL, progression after receiving at least 2 lines of chemotherapy, and ineligible for or failed autologous stem cell transplant. Shuster shared a flow chart depicting the study status for JULIET, which had a data cutoff of March 8, 2017. Of the 147 patients who initially enrolled in the trial, 43 patients left the trial prior to infusion and 5 were pending infusion. Of the 99 who received a single CTL019 infusion, 81 were evaluable for response, 89 had received bridging chemotherapy, and 92 had received lymphodepleting chemotherapy (73% received fludarabine 25 mg/m2 and cyclophosphamide 250 mg/m2/day for 3 days; 19% received bendamustine 90 mg/m2/day for 2 days).

The best ORR in the 81 patients was 53%, with 40% achieving a CR and 14% achieving a PR. The 3-month ORR was 38% (32% CR + 6% PR) and ORR at 6 months was 37% (30% CR + 7% PR). "The durability off the CTL019 response is shown by the stability between the 3- and 6-month response rates," Schuster pointed out, adding that the 3-month response hints at a more long-term benefit of this treatment.

Subgroup analysis also showed consistent ORR across the various cohorts:

- All patients: 53.1% (95% CI, 41.7%-64.3%)
- Age
  - <65 years: 50.0% (95% CI, 37.2%-62.8%)
  - ≥65 years: 64.7% (38.3%-85.8%)
- Gender
  - Female: 62.1% (95% CI, 42.3%-79.3%)
  - Male: 48.1% (95% CI, 34.0%-68.5%)
- Prior neoplastic therapy
  - ≤2 lines: 53.7% (95% CI, 37.4%-69.3%)
  - >2 lines: 52.5% (95% CI, 36.1%-68.5%)

"The median duration of response and median overall survival had not been reached at data cutoff," Schuster said. He also indicated that 74% of patients were relapse free at 6 months and almost all patients who had a CR at 3 months remained relapse-free. "Patients who responded with either a CR or a PR did not proceed to receive allogenic- or auto-stem cell transplant," he added.

Overall, 86% of patients had grade 3 or 4 adverse events (AEs). Cytokine release syndrome (CRS) occurred in 58% of infused patients: 15% were grade 3 and 8% were grade 4. About 15% of patients received anti-IL6 therapy (tocilizumab) for CRS management, with good response, and 11% of patients received

corticosteroids. Other grade 3 or 4 AEs included neurologic AEs (12%, managed with supportive care), cytopenias lasting longer than 28 days (27%), infections (20%), and febrile neutropenia (13%). Three patients died within 30 days of infusion, all due to disease progression. No deaths were attributed to CTL019, CRS, or neurologic events.

Of the 26 (26%) patients in the study who received outpatient infusion, 20 (77%) remained on outpatient status for at least 3 days following infusion, "which means tisagenlecleucel can be safely administered in both the inpatient and the outpatient settings," Schuster concluded.

Speaking during a press briefing in advance of the annual meeting, 2017 ASH President Kenneth C. Anderson, MD, highlighted the international scope of the JULIET trial, which he said indicates a much broader reach of this treatment.

The future plans for JULIET include:

- Ongoing global regulatory submissions
- Large-scale production of tisagenlecleucel
- A 22-day manufacturing time in the commercial setting

The second study was a 15.4-month follow-up on ZUMA-1, which is designed to evaluate axicabtagene ciloleucel (Axi-cel, Yescarta) in patients with refractory aggressive NHL.[2] Axi-cel became the second approved CAR T-cell treatment, in October, for adult patients with DLBCL. The results were presented by Sattva S. Neelapu, MD, professor in the Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center. The results were simultaneously published in the *New England Journal of Medicine*.[3]

The primary analysis of ZUMA-1 demonstrated positive results, Neelapu said, with an ORR of 82% and a CR rate of 54% after a single infusion of axicel. The treatment had a manageable safety profile as well: grade ≥3 CRS and neurologic events were generally reversible and reported in 13% and 28% of patients, respectively. "At a median follow-up of 8.7 months, 44% of patients in ZUMA-1 had an ongoing response," Neelapu indicated.

The study population included patients with refractory DLBCL (n = 77), and transformed follicular lymphoma or primary mediastinal large B cell lymphoma (total n = 24). Patients were treated with cyclophosphamide (500 mg/m2) plus fludarabine (30 mg/m2) for 3 days to condition the body prior to treatment with 2x106 CAR-positive T cells/kg.

"While the CAR T-cell product was successfully manufactured in 99% of enrolled patients, only 91% received the infusion," Neelapu said. Eligibility criteria included:

- Refractory disease, defined as progressive disease or stable disease as best response to last line of therapy
- Relapse ≤12 months after autologous stem-cell transplant
- Prior anti-CD20 antibody and an anthracycline-containing regimen

The primary endpoint was ORR and secondary endpoints included duration of response (DOR), overall survival (OS), and incidence of AEs. A key exploratory endpoint was to investigate the mechanisms of resistance using posttreatment tumor biopsies obtained at time of relapse or progression.

"The median duration of response and median overall survival had not been reached at data cut off. Patients who responded with either a [complete response] or a [partial response] did not proceed to receive allogenic- or auto-stem cell transplant."

—Stephen Schuster, MD, Perelman School of Medicine

"To date, no patients have been lost to follow-up, and all patients who are alive remain in disease and survival follow-up," Neelapu told the audience.

Following analysis of results from the trial, at a data cut-off date of August 11, 2017, which was a 15.4-month follow-up, the best ORR was 82%, with a CR rate of 58%. Neelapu noted that patients who had a PR at the first tumor assessment (which was 1 month post infusion) had a CR up to 15 months post infusion, without need for additional treatment. The median time for conversion from PR to CR was 64 days (range, 49-424).

Overall DOR was 11.1 months (range, 3.9-not reached), CR was not reached, and PR was 1.9 months (range, 1.4-2.1). "Forty-three percent of phase 1 patients have an ongoing CR at 24 months," he said. The following are the 15.4-month survival updates from the study:

- Median progression-free survival: 5.8 months (range, 3.2-not reached)
- Median OS: not reached (range, 12.0-not reached)

With respect to AEs, Neelapu said that 95% of patients had grade 3 or higher AEs (43% of which were serious adverse events [SAEs]) in the primary analysis, which increased to 97% in the updated analysis (46% SAEs). Grade 3 or higher CRS was noted in 13% of patients following the primary analysis and 12% with the update; 28% of patients experienced neurologic toxicities at the point of the primary analysis, which increased to 31% by the time of the current updated analysis. Grade 5 AEs were also documented in a small proportion of patients. Further, infections were the most common new-onset treatment-emergent SAEs at 6 months, but were resolved by the time of data cut off in August.

Biomarker clues were investigated by the ZUMA-1 researchers who identified several serum biomarkers associated with neurologic events and CRS of grade 3 or higher (including IL-6, IL-10, IL-15, IL-2Rα, and granzyme B). IL-2, granulocyte-macrophage colony-stimulating factor, and ferritin were significantly associated only with neurologic events of grade 3 or higher.

SATTVA S. NEELAPU, MD, ABOVE, AND STEPHEN SCHUSTER, MD, OFFERED UPDATES ON CAR T-CELL THERAPIES.

Based on these findings, Neelapu concluded that although a median DOR or OS had not been reached, durable response was observed in both patients who had detectable persistent CAR T cells and those who did not, which he said could be attributed to CD19 loss or immune checkpoint activation, according to some preliminary observations by the study group. ◆

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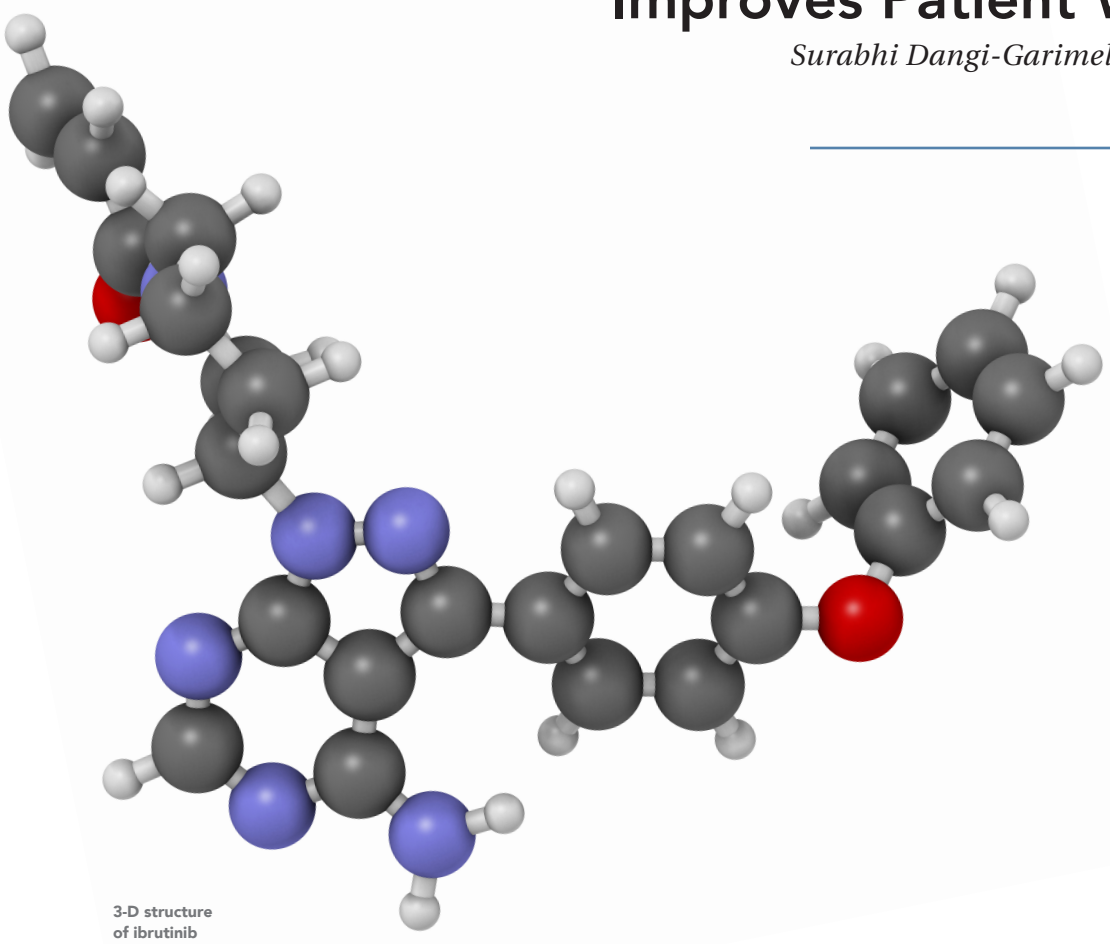
CLINICAL

Single-Agent Ibrutinib Promising in MCL and CLL, Improves Patient Well-Being

Surabhi Dangi-Garimella, PhD



3-D structure of ibrutinib

THREE STUDIES PRESENTED AT the 59th Annual Meeting and Exposition of the American Society of Hematology (ASH) shared progress on the oral Bruton's tyrosine kinase inhibitor, ibrutinib (Imbruvica), in the treatment of relapsed/refractory mantle cell lymphoma (MCL) and as a single agent in chronic lymphocytic leukemia (CLL).

The MCL results were the results of a 3.5-year follow-up of a pooled analysis of 370 patients with relapsed/refractory MCL who were treated with ibrutinib as part of 3 open-label studies: SPARK, RAY, and PCYC-1104. This longer-term follow-up, which included additional exposure to treatment, was conducted in 87 patients across the 3 studies who enrolled in the long-term access study, CAN3001, a phase 3b open-label study.[1]

Patients received 560-mg ibrutinib orally, once daily, until progressive disease or unacceptable toxicity. Patients in the SPARK study were required to have received both rituximab (Rituxan) and bortezomib (Velcade), while those in the RAY study had to have prior treatment with rituximab. Only those patients who continued to benefit from ibrutinib therapy at end of the study could enroll in CAN3001. Crossover patients were excluded from the final pooled analysis. The study evaluated investigator-assessed tumor response, progression-free survival (PFS), and overall survival (OS). The median duration of follow-up in the pooled data set was 41.1 months (95% CI, 37.3-42.5), and the median treatment exposure was 11.1 months (range, 0.03-72.1). Fifty-four of the 87 (62.1%) patients enrolled in CAN3001 remain on ibrutinib and had received at least 2 prior lines of treatment (LOT).

At the 41-month follow-up check, 26.5% patients had achieved complete response (CR). The median PFS was 13.0 months in the overall patient population, 33.6 months (range, 19.4-42.1) in patients with 1 prior LOT, and 46.2 months (range, 42.1-not estimable) in patients achieving a CR. The median OS was 26.7 months:

- 53% patients were alive at 2 years (95% CI, 0.47-0.58)
- 45% patients were alive at 3 years (95% CI, 0.39-0.50)
- 37% patients were alive at 5 years (95% CI, 0.25-0.49)

Grade 3 or greater treatment-emergent adverse events (TEAEs) occurred in 295 (79.7%) patients, with the new-onset events decreasing after the first year, the authors reported. The most common grade ≥ 3 TEAEs were neutropenia (17.0%), thrombocytopenia (12.2%), pneumonia (11.9%), anemia (9.5%), atrial fibrillation (5.9%), and hypertension (5.1%)—a majority were more common during the first year of ibrutinib treatment. Treatment-emergent severe adverse events (SAEs) occurred in 229 (61.9%) patients, and new-onset SAEs decreased over time.

Another presentation at the meeting reported results from a crossover study that compared single-agent ibrutinib (RESONATE-2) and chemoimmunotherapy regimens in treatment-naïve patients with patients with CLL from published studies with the following regimens:[2]

- Fludarabine + cyclophosphamide + rituximab (FCR) from CLL8 (FCR-CLL8), published in *The Lancet*[3]
- Bendamustine + rituximab (BR) and FCR from CLL10 (FCR-CLL10), published in *Lancet Oncology*[4]
- Obinutuzumab (Gazyva) + chlorambucil (G-Clb) and rituximab + Clb (R-Clb) from CLL11, published in *The New England Journal of Medicine*[5]
- Ofatumumab + Clb (Ofa-Clb) from COMPLEMENT-1, published in *The Lancet*[6]

Limitations of the current analysis, the authors write, were the lack of available patient-level data from the chemoimmunotherapy studies and differences in study design and patient eligibility criteria.

The median age across the studies ranged from 61 to 74 years; older patients usually enrolled in studies with ibrutinib, G-Clb, or R-Clb. Median CIRS scores ranged from 1 to 9, with lower comorbidity scores for patients treated with BR, FCR-CLL10, and FCR-CLL8.

Treatment with single-agent ibrutinib, the authors report, was associated with longer PFS compared with chemoimmunotherapy regimens; particularly, PFS with ibrutinib compared favorably to chemoimmunotherapy studies that also excluded patients with del(17p) (BR and FCR-CLL10) and those that enrolled older patients with comorbidities (G-Clb, R-Clb, and Ofa-Clb). In patients with unmutated *IGHV*, the PFS hazard ratio (HR) compared with chlorambucil was 0.08 (95% CI, 0.04-0.17) for ibrutinib, 0.23 (95% CI, 0.16-0.34) for G-Clb, and 0.54 (95% CI, 0.38-0.76) for R-Clb. In patients with del(11q), the PFS HR compared with chlorambucil was

0.02 (95% CI, 0.005-0.11), 0.37 (95% CI, 0.17-0.81), and 0.99 (0.49-2.03) for ibrutinib, G-Clb, and R-Clb, respectively. PFS rates across baseline groups were favorable with ibrutinib, compared with BR or FCR regimens in CLL10, especially in patients who had advanced disease, bulky lymph nodes, unmutated *IGHV*, and del(11q).

OS with single-agent ibrutinib favored chemoimmunotherapy in studies with older or less fit patients; however, compared with chlorambucil, OS with ibrutinib alone was better relative to Ofa-Clb, R-Clb, and G-Clb.

Despite its limitations, the authors propose that the results of their cross-trial comparison suggest that ibrutinib may potentially eliminate the need for chemotherapy in some patients with treatment-naive chronic lymphocytic leukemia.

The overall rate of grade ≥3 adverse events (AEs) for chemoimmunotherapy regimens was highest with FCR, followed by BR and chlorambucil-based regimens; the rate was similar for ibrutinib and G-Clb despite the longer data collection period for ibrutinib. The rate of grade ≥3 infections varied by study and ranged from 9% with Ofa-Clb to 25% with ibrutinib to 40% with FCR-CLL10. Rates of grade ≥3 cytopenias were generally lower with ibrutinib compared with chemoimmunotherapy.

Despite its limitations, the authors propose that the results of their cross-trial comparison suggest that ibrutinib may potentially eliminate the need for chemotherapy in some patients with treatment-naïve CLL.

Quality-of-life observations from the phase 3 RESONATE-2 study—conducted in older, treatment-naïve patients with CLL or small lymphocytic leukemia—were also presented at the ASH meeting.[7] With respect to clinical outcomes, single-agent ibrutinib in this patient population reduced the risk of disease progression or death by 84%, compared with chlorambucil, at a median follow-up of 18.4 months.

Patients 65 years or older were randomized to receive 420-mg ibrutinib once daily until progressive disease or chlorambucil for up to 12 months. Patients who progressed on chlorambucil had the option of receiving second-line ibrutinib. The various patient-reported outcomes (PROs) that were measured included FACIT (Functional Assessment of Chronic Illness Therapy)-Fatigue, EQ-5D-5L, Q-TWiST, and EORTC QLQ-C30 global health status.

The median follow-up among 269 patients, who had initiated therapy due to progressive marrow failure (38%), lymphadenopathy (37%), splenomegaly (30%), fatigue (27%), or night sweats (25%), was 35.7 months with ibrutinib and 34.4 months with chlorambucil. Ibrutinib treatment resulted in significantly longer PFS compared with chlorambucil (median, not reached vs 15.0 months). Additionally, there was an 87% reduction in risk of progression or death with ibrutinib (HR, 0.130; 95% CI, 0.081-0.208).

Importantly, for this particular study, the authors report greater and sustained improvements in PROs, which improved over time:

- FACIT-F ($P = .0021$) and EQ-5D-5L Visual Analogue Scale ($P = .0004$) by repeated measures. Crossover patients from the chlorambucil arm saw improved PROs.
- Approximately 87% of patients on ibrutinib (vs 52% on chlorambucil) had decreased/normalized lymphadenopathy within 2 months; this effect was sustained through 36 months.
- Disease symptoms, including fatigue and night sweats, improved more frequently with ibrutinib compared with chlorambucil. Sustained hematologic improvement was observed with ibrutinib for hemoglobin (90% vs 45%; $P < .0001$) and platelets (83% vs 46%; $P = .0032$) among patients who had baseline cytopenia.
- Medical resource utilization burden was less with ibrutinib in the first year (use of intravenous immunoglobulin, growth factors, or transfusions) and continued to decrease.
- During the first year of treatment, patients on ibrutinib presented with less grade ≥3 neutropenia (8% and 18%) and anemia (6% and 8%) compared with chlorambucil.
- Other common grade ≥3 AEs were pneumonia (5% and 2%) and hypertension (4% and 0%).

Based on their Q-TWiST analysis at a median follow-up of 18.4 months, the authors report that the mean time spent without symptoms of disease progression or grade 3-4 treatment toxicity was longer with ibrutinib (501 vs 351 days; 95% CI, 109, 193). ◆

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Attendees walk in the main hall at the Saturday sessions, December 9, 2017, at the American Society of Hematology 59th Annual Meeting and Exposition.

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CLINICAL

Clonal Expansion and Aging Fuel the Development of Neoplasms, Say Experts at ASH

Surabhi Dangi-Garimella, PhD

AT A JOINT SYMPOSIUM between the American Society of Hematology and the European Hematology Association, 2 hematologists shared their own research findings, and others from the field, on somatic mutations in hematopoietic cells and clonal expansion, which are acquired and correlated with aging. These mutations, also defined as clonally-restricted hematopoiesis, are associated with an increased risk of myeloid or lymphoid neoplasms as well as increased cardiovascular and all-cause mortality.

Benjamin L. Ebert, MD, PhD, of the Division of Hematology, Brigham and Women's Hospital, Boston, Massachusetts, was the first to present. He explained that full-grown malignancies result from somatic mutations and the expansion of mutated hematopoietic stem cells, a condition described as myelodysplastic syndrome.[1] Ebert pointed out an important question to answer: "What is the percent of individuals who accumulate the mutations but do not develop a malignancy?"

Ebert noted that X chromosome inactivation is central to our understanding of the pathogenesis of hematological malignancies, and that evidence from several research groups has shown skewed X-inactivation patterns in multiple lineages and the stem cell origin for these diseases.[2] Additionally, evidence presented by other labs has indicated the presence of recurrent somatic mutations in *TET2* with X-inactivation skewing. These mutations, he noted, were specific for individuals who had clonal hematopoiesis and were nonmalignant.[3]

The existing trend, Ebert said, is to look for specific somatic mutations in myeloid malignancy by analyzing the peripheral blood cells (PBCs) of individuals. This was described in a paper published by his research group in 2014,[4] wherein PBCs of more than 17,000 individuals were analyzed for single-nucleotide variants that are commonly mutated in hematologic cancers. An age-related phenomenon was observed in the samples: Detectable somatic mutations were rare in those younger than 40 years and were more frequently observed in those older than 70 years. A majority of these variants were in epigenetic regulators like *TP53*, *TET2*, and *ASXL1*.

"This clonally restricted hematopoiesis increases an individual's risk of developing a hematologic malignancy," Ebert said.

A review published by Ebert's group in 2015 described the phenomenon of clonal hematopoiesis of indeterminate potential (CHIP)[5]. The authors noted that while age-related increase in mutations is a normal occurrence, mutations associated with myelodysplastic syndrome (MDS) in a cytopenic patient, when there are no other signs of MDS, can lead to diagnostic uncertainty.

He explained that 4 types of clonal hematopoiesis have been noted:

- Unknown drivers
- Stem cell attrition
- Clonal drift
- Rare mutations

There is a significant amount of unknown, Ebert explained, adding that the field is evolving rapidly as researchers try to define whether clonal hematopoiesis, in the absence of cytopenias, can convey health risks, and whether prophylactic interventions can be developed.

A recent study by his group does point to an association between CHIP and the development of myeloid malignancies.[6] Of the 401 patients who received autologous stem-cell transplants for their lymphoma treatment, patients with CHIP had significantly lower 10-year overall survival (30.4%) compared with patients without CHIP (60.9%; $P<.001$).

Several studies have also noted an increased risk of therapy-related myeloid neoplasms, Ebert said. "Patients with CHIP have reduced survival, partially due to therapy-related malignancies as well as the development of cardiovascular [CV] disease," he pointed out. Ebert's group, in their recent paper in the *New England Journal of Medicine*,[7] showed that CHIP can cause a significant increase in patient risk of both coronary artery disease (HR, 2.0; 95% CI, 1.2-3.4; $P=.018$) and stroke (HR, 2.6; 95% CI, 1.4-4.8; $P=.003$). Additionally, in 2 early-onset myocardial infarction cohorts, the presence of CHIP was associated with a high odds ratio for CV disease. The group also identified a few causative mutations—in the *DNMT3A, TET2, ASXL1*, and *JAK2* genes—that could lead to coronary artery disease.

"CHIP is associated with increased overall mortality," Ebert concluded.

Representing the European perspective was George S. Vassiliou, MD, PhD, of the Department of Hematology, Wellcome Trust Sanger Institute, in Hinxton, Cambridge, United Kingdom.

"Myeloid neoplasm can shift grades to lead to acute myeloid leukemia [AML]," Vassiliou said, adding that 50 genes of varying frequencies with known associations with clinical symptoms have been identified. "The number of coding mutations, however, are small: There are 10 known mutations in adult MDS and 13 in adult AML," which are numbers comparable with mutations in normal hematopoietic stem cells in an older individual.

Vassiliou explained that while some cancers, such as breast cancer, have a large number of mutagens, acute myeloid neoplasms have just 2 known signatures. Accumulation of mutations in 1 of 6 genes leads to clonal hematopoiesis; accumulation of additional mutations following exposure to various insults results in additional mutations that can lead to the development of myeloid syndromes in these individuals and can eventually lead to AML. "However, not all mutations lead to neoplasms," Vassilou said.

Age-related clonal hematopoiesis is known to be associated with hotspot mutations. About 10% of individuals have mutations in specific hotspots, to which are added age-related changes in driver mutations.[8] In individuals above age 70, mutations are more common in the spliceosome genes, which are associated with MDS. Vassilou explained that these spliceosome gene mutations drive clonal expansion under selection pressures of the aging hemopoietic system, and they can explain the high incidence of clonal disorders associated with these mutations in individuals of advanced age.

"Can we predict who will develop a myeloid malignancy?" Vassilou asked.

He then described an ongoing study in which he is involved, the European Prospective Investigation into Cancer and Nutrition Study. It is designed to investigate the relationships among diet, nutritional status, lifestyle, and environmental factors, on the one hand, and the incidence of cancer and other chronic diseases on the other. The study, which has more than half a million participants across 10 European countries, has a 15-year follow-up period.

The discovery cohort of the study includes 95 individuals with AML and the validation cohort has 29 with AML. Across age groups, the prevalence of clonal hematopoiesis in the pre-AML population was 73%, compared with 33% in the control population ($P<.001$). Preliminary study discoveries indicate "that splicing gene mutations accumulate at a younger age in the pre-AML population and could be predictive of malignancy," Vassilou said. ◆

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CLINICAL

Treatment-Free Remission and Preventing Cardiotoxicity: The Future of CML Care

Surabhi Dangi-Garimella, PhD

TYROSINE KINASE INHIBITORS (TKIs) have come a long way in the treatment of chronic myelogenous leukemia (CML), so much so that survival in this patient population can be compared with the healthy population. However, recent findings on adverse events (AEs) associated with these agents have raised concerns about the long-term impact of TKIs on a patient's quality of life.

At the 59th Annual Meeting & Exposition of the American Society of Hematology in Atlanta, Georgia, physicians shared current knowledge on cardiovascular toxicities of TKIs as well as the potential for treatment-free remission with these agents.

François-Xavier Mahon, MD, PhD, of Bordeaux Segalen University, Bordeaux, France; reviewed and summarized some of the recent studies related to TKI cessation in patients with deep molecular response, which have raised the idea of treatment-free remission (TFR).

During his talk, "Treatment-Free Remission in CML: Who, How, and Why?," Mahon said that the emerging goal of leukemia management is treatment cessation. "Studies have shown that this is feasible," he added.

A recent study in *Cancer Science*, for example, evaluated the conditions important for dasatinib cessation in patients with CML who maintained a deep molecular response for at least 2 years.[1] The study documented a 12-month treatment-free survival in about 63% of patients and tracked their molecular response as being a much smaller increase in natural killer cells.

A much earlier study by Mahon and some of his colleagues, published in 2001, showed that certain CML cell lines that had developed resistance to specific agents reacquired their sensitivity to the agent when left untreated for a specified period of time.[2] A large collaborative study, authored by researchers from various institutions in France, found that the loss of a major molecular response (MMR)—in this case with imatinib mesylate in patients with CML—was a criterion indicating the safety of restarting therapy in patients who had a complete molecular response.[3]

"The question is, Why should we stop treatment?" Mahon asked.

He then listed a number of reasons that support stopping unnecessary treatment with TKIs:

- Off-target effects
- Severe AEs, including pulmonary arterial hypertension (PAH) and pleural effusion
- Cardiovascular toxicity
- Contraindication in pregnant women
- Effects on fertility
- Growth alteration in children

"In addition to the patient's quality of life, there's increasing concern about the pharmacoeconomics of the lifelong use of TKIs," Mahon added.

Several trials were designed to test this hypothesis:

- The STIM1 study evaluated the safe discontinuation of imatinib in patients with CML who have had undetectable minimal residual disease. Median molecular follow-up was 77 months after treatment discontinuation. The trial authors concluded that imatinib can be safely discontinued in patients with a sustained deep molecular response with no late molecular recurrence.[4]
- The ENESTfreedom study demonstrated proof-of-principle with frontline nilotinib in patients with Philadelphia chromosome–positive CML. At 96 weeks from the start of TFR phase, 67 of 126 patients were in a treatment-free regimen.[5]
- The EURO-SKI study is a global trial designed to assess the duration of MMR after halting TKI treatment. Of the 755 participants on this trial, Mahon said that the probability of being off-treatment is 50% in the context of MMR.

Mahon had several recommendations for stopping TKI treatment in good-responder patients who are outside of a clinical trial:

- Key prerequisites
  - Creating a national or international registry
  - Patient should not have a history of resistance to treatment
  - Strict molecular monitoring; need for a certified laboratory to express the results
- Patients
  - Chronic-phase CML who have been treated with TKIs for at least 5 years
- Molecular monitoring: monthly for the first 12 months, every 2 months in the second year, and every 3 months thereafter

He added, however, that instead of completely halting treatment, dose reduction is also an option in these patients.

Javid Moslehi, MD, of Vanderbilt School of Medicine, Nashville, Tennessee, reviewed what is currently known about the cardiovascular toxicities of TKIs and discussed potential mechanisms underlying cardiovascular AEs.

"I am a cardio-oncologist by training," Moslehi said, "and most of my clinic involves managing toxicities from cancer treatment." He indicated that both older and newer anticancer therapies seem to have this cardiovascular effect, such that patients present with a wide range of myocardial toxicities.

"Interestingly, classic cardiovascular risk factors have been shown to be risk factors for cancer as well," he noted.

Moslehi shared with the audience a detailed slide that listed some of the commonly used anticancer agents, many of which were TKIs, and their associated cardiovascular effects:

- Anthracyclines and radiation: heart failure and coronary artery disease
- Human epidermal growth factor 2–targeted therapies: cardiomyopathy
- Immunotherapies: myocarditis
- CML TKIs: PAH, atherosclerosis
- Bruton's tyrosine kinase inhibitors: arrhythmia, atrial fibrillation

He then compared the TKI nilotinib with imatinib; in addition to vascular and cardiovascular events associated with nilotinib, imatinib also causes hyperglycemia, which is also a known risk factor for cardiovascular events.

Moslehi pointed out the lack of clarity, at least among oncologists, on the cardiovascular impact of TKIs. "We also need to get better at patient risk stratification. A personalized approach is needed for toxicity assessment," he said, providing the audience with some clinical perspectives:

- The National Comprehensive Cancer Network Guidelines do not provide much insight.
- We need to think of baseline cardiovascular risk factors in patients being treated with agents that have cardiovascular effects. These patients also need regular follow-up after treatment initiation.
- Additionally, patients need to follow the ABCDE steps for heart and vascular wellness (aspirin, blood pressure, cholesterol/avoiding cigarettes, diet/diabetes screening, exercise).

"Education is vital," Moslehi said. "We need to educate both patients and providers [about these cardiovascular risks]." ◆

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#1 PRESCRIBED THERAPY IN FRONTLINE* AND PREVIOUSLY TREATED CLL[1†]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA® (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS[2]

*Based on market share data from IMS from November 2016 to April 2017.
†Based on market share data from IMS from May 2014 to April 2017.

CLL
SLL

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

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

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®.

Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

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

Monitor patients closely and treat as appropriate.

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

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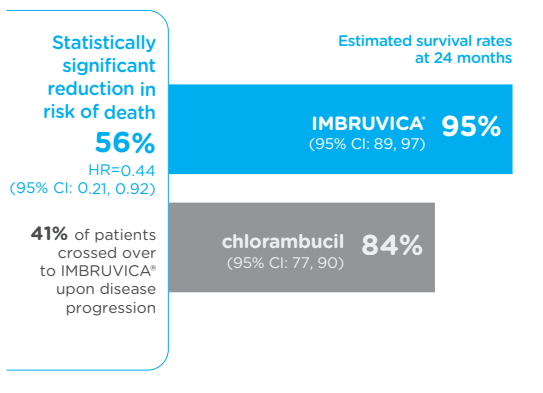
RESONATE™-2 FRONTLINE DATA

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

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

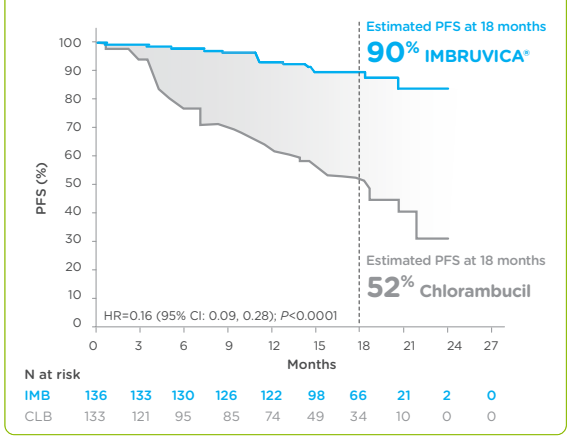


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not reached vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

RESONATE™-2 Adverse Reactions ≥15%

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

of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%), neutropenia (61%), diarrhea (43%), anemia (41%), musculoskeletal pain (30%), rash (30%), bruising (30%), nausea (29%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%), thrombocytopenia (16%), and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9 % (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

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

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%), pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

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

DRUG INTERACTIONS

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

CYP3A Inhibitors: Dose adjustment may be recommended.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2017. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

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

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

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

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

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

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy *[see Clinical Studies (14.5) in Full Prescribing Information].*

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

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

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

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

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

* One patient death due to histiocytic sarcoma.

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

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

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

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

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

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

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

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

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

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

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1

IMBRUVICA® (ibrutinib) capsules

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

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

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

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

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

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

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 1118) and 63 patients with previously treated MZL (Study 1121).

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

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

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

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection Sinusitis Pneumonia* Skin infection*	19 19 14 14	0 0 6 2
Respiratory, thoracic and mediastinal disorders	Epistaxis Cough	19 13	0 0
Nervous system disorders	Dizziness Headache	14 13	0 0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (N=63)

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

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

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

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

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

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

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

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

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

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue Pyrexia Edema peripheral	57 17 12	12 5 0
Skin and subcutaneous tissue disorders	Bruising* Rash*	40 12	0 0
Gastrointestinal disorders	Diarrhea Stomatitis* Nausea Constipation	36 29 26 12	10 2 0 0
Musculoskeletal and connective tissue disorders	Muscle spasms Musculoskeletal pain*	29 14	2 5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia* Upper respiratory tract infection Sepsis*	21 19 10	10 0 10

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4(%)
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	14 12	0 2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

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

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

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

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

DRUG INTERACTIONS

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

Examples[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and troleandomycin.

Examples[a] of moderate CYP3A inhibitors include: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

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

Patients with B-cell Malignancies: *Posaconazole:* Reduce IMBRUVICA dose to 140 mg once daily during coadministration with posaconazole at doses of no more than 200 mg BID *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Avoid the coadministration of IMBRUVICA with posaconazole at doses of greater than 200 mg BID.

Voriconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any dose of voriconazole *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Other Strong Inhibitors: Avoid concomitant administration of IMBRUVICA with other strong CYP3A inhibitors. Alternatively, interrupt IMBRUVICA therapy during the duration of strong CYP3A inhibitors if the inhibitor will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Moderate Inhibitors: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any moderate CYP3A inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor patients taking concomitant strong or moderate CYP3A inhibitors more frequently for adverse reactions of IMBRUVICA.

Patients with Chronic Graft versus Host Disease: *Moderate CYP3A Inhibitor:* Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]* for patients coadministered IMBRUVICA with any moderate CYP3A inhibitor.

Strong CYP3A Inhibitors: Reduce IMBRUVICA dose to 280 mg once daily for patients coadministered IMBRUVICA with

- posaconazole immediate-release tablet 200 mg BID or
- posaconazole delayed-release tablet 300 mg QD or
- voriconazole any dose

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]*

Avoid concomitant administration of IMBRUVICA with posaconazole at higher doses and other strong CYP3A inhibitors. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA therapy during the duration of the inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort[b].

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[b] The induction potency of St. John's wort may vary widely based on preparation.

USE IN SPECIFIC POPULATIONS

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

CLINICAL

Ibrutinib Is More Effective Than Stem-Cell Transplant in Patients With Form of Chronic Leukemia

Jaime Rosenberg

AN ANALYSIS PRESENTED at the 59th Annual Meeting of the American Society of Hematology in Atlanta, Georgia, showed that ibrutinib has higher rates of overall survival (OS) and progression free survival (PFS) in the treatment of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) with 17p deletion (del(17p)).

Before the emergence of targeted therapies, allogeneic HSCT was the preferred therapy for R/R CLL del(17p). Now, treatment options such as oral ibrutinib provide the opportunity for significant OS and PFS with the convenience of being non-invasive. However, ibrutinib is not considered curative; meanwhile, HSCT has curative potential but has a high upfront cost, potential transplant-related morbidity and mortality, and potential relapse, according to the authors.

"Both treatments are expensive with relative differences in cost of treatment and supportive care management," the authors wrote. "Considering these different profiles, we performed cost-effectiveness and cost-utility analyses of ibrutinib versus HSCT in R/R CLL del(17p) from a US payer perspective."

"The importance of this study is to provide clinical and economic information to decision makers."

—Nimer Alsaid, PhD

Three-year and lifetime horizon Markov models were constructed defining 3 health states: PFS with embedded substates specifying whether a patient is on or off therapy, progression, and death. The cost of ibrutinib was determined from RED BOOK; costs of HSCT procedure, preconditioning treatment, and post-procedural adverse effects were estimated from published prediction equations and national claims databases.

The authors applied a 3% discount rate when survival exceeded 1 year. Following extrapolation to the 3-year and lifetime horizons, the life years (LY) and quality adjusted LY (QALY) were estimated for each treatment. In addition, total treatment costs, cost differentials, and the incremental cost effectiveness (ICER) and incremental cost utility ratios (ICUR) were determined. The base case analyses were validated by probabilistic sensitivity analyses (PSA).

The 3-year Markov model showed ibrutinib yielded a cost savings of $48,642 (PSA: $48,678), incremental gains of 0.23 (PSA: 0.22) LY and 0.20 (PSA: 0.19) QALY, bearing an ICER of savings of –$211,487 (PSA: –$221,246) per LY gained and an ICUR of savings of –$243,210 (PSA: -$256,200) per QALY gained. However, the lifetime Markov model, showed that ibrutinib yielded an incremental cost of $25,802 (PSA: $23,317), incremental gains of 0.12 (PSA: 0.09) LY and 0.13 (PSA: 0.11) QALY, yielding an ICER of $215,016 (PSA: $259,077) per LY gained and an ICUR of $198,476 (PSA: $211,972) per QALY gained.

Over a 3-year period, ibrutinib succeeds in OS and PFS over HSCT in the treatment of patients with R/R CLL del(17p) and has the benefit of being clinically superior in combined efficacy and safety at a lower cost. However, it lacks curative potential. Over a lifetime, ibrutinib still proved to be superior in OS and PFS over HSCT, but is no longer cost-saving as treatment costs continue, and attains cost-effectiveness at a willingness-to-pay threshold of approximately $260,000, the authors wrote.

"The importance of this comparative study is to provide clinical and economic information to decision makers that help them to make decisions about adding or removing interventions from formulary and/or about reimbursement strategies," said author Nimer Alsaid, PhD, Center for Health Outcomes and PharmacoEconomic Research, University of Arizona, in an interview with *The American Journal of Managed Care®*. ◆

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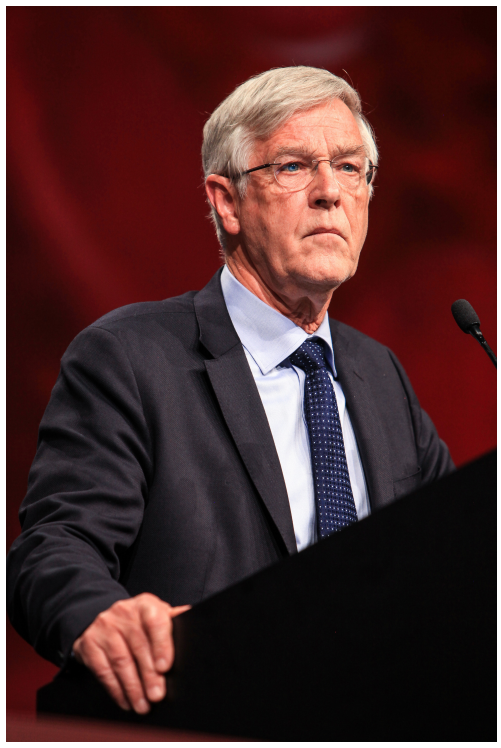
CLINICAL

New Treatment Paradigm Supersedes ABVD in Advanced Hodgkin Lymphoma: The ECHELON-1 Study

Surabhi Dangi-Garimella, PhD



Joseph M. Connors, MD, speaking at the 59th Annual Meeting and Exposition of the American Society of Hematology.

PHASE 3 RESULTS FROM the ECHELON-1 study, presented at the 59th Annual Meeting & Exposition of the American Society of Hematology, showed superior modified progression-free survival (mPFS) after adding the modified anti-CD30 antibody brentuximab vedotin to doxorubicin, vinblastine, and dacarbazine (AVD) in patients with advanced Hodgkin lymphoma (HL). This presents a significant change in the standard frontline regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), which has not been modified for over 40 years, since it was first described, according to presenting author Joseph M. Connors, MD, medical oncologist, BC Cancer Agency, University of British Columbia, Canada.

About 30% of patients with advanced-stage HL have relapsed or refractory disease following frontline ABVD. Add to that the pulmonary toxicity associated with bleomycin, which may then be dropped off from later cycles of chemotherapy.

Connors then shared the phase 2 results of ECHELON-1, which documented a 3-year PFS of 58% and a 3-year overall survival (OS) of 73%.[1] "Of the 34 patients who had a complete response, 47% were progression free at 53 months," he added. "Several studies have demonstrated that intensifying the ABVD regimen in these advanced-stage patients does not provide any survival advantage," Connors said. Therefore, the considerations for their study design for the new regimen included:

- OS advantage
- Duration of follow-up
- Impact on fertility and short- and long-term organ damage
- Economics, especially in the context of supportive care such as the need for growth factors

Patients enrolled in the open-label, global (218 study sites in 21 countries) ECHELON-1 study were randomized 1:1 to receive A+AVD (brentuximab vedotin 1.2 mg/kg, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2) (n = 664) or ABVD (doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2) (n = 670) on days 1 and 15 of up to six 28-day cycles. "Patients with a [positron emission tomography] (PET) scan Deauville score of 5 after cycle 2 could switch to alternative therapy at the treating physician's discretion," Connors said.

Patients (n =1334) were stratified by region (Americas vs Europe vs Asia) and International Prognostic Score (0-1 vs 2-3 vs 4-7). Toward the end of the study, the independent data monitoring committee recommended primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) for newly randomized patients receiving A+AVD based on a higher incidence of febrile neutropenia in that arm. The primary end point was mPFS (defined as time to progression, death, or evidence of incomplete response followed by subsequent anticancer therapy) determined by independent review facility assessment.

At a median follow-up of 24.9 months (range, 0-49.3), the 2-year rate of mPFS was 82.1% in the A+AVD group (95% CI, 78.7-85.0) compared with 77.2% (95% CI, 73.7-80.4) in the ABVD group. The hazard ratio for progression, death, or modified progression, 0.77 (95% CI, 0.60 to 0.98; $P = .03$), corresponded with a 23% risk reduction.

Fewer patients in the A+AVD arm (n = 117) had events of progression, death, or modified progression compared with the ABVD arm (n = 146). The trial documented the following secondary end points for A+AVD compared with the ABVD arm:

- Complete response rate at the end of the randomized regimen: 73% versus 70% ($P = .22$)
- Objective response rate at the end of the randomized regimen: 86% versus 83% ($P = .12$)
- PET Deauville score 1 or 2 after frontline therapy: 85% versus 80% ($P = .03$)
- PET Deauville score of 1, 2, or 3 after cycle 2: 89% versus 86% ($P = .18$)

Neutropenia was reported in 58% of patients receiving A+AVD and 45% receiving ABVD (febrile neutropenia in 19% and 8%, respectively), but discontinuations due to neutropenia or febrile neutropenia were low in both arms. Grade ≥3 infections were more common in the A+AVD arm (18%) than the ABVD arm (10%). In patients receiving A+AVD, primary prophylaxis with GCSF (n = 83) reduced febrile neutropenia from 19% to 11% and grade ≥3 infections and infestations from 18% to 11%. Peripheral neuropathy (PN) occurred in 67% of patients receiving A+AVD and 43% receiving ABVD; 67% of patients experiencing PN in the A+AVD arm had resolution or improvement of PN at last follow-up. Pulmonary toxicity was more frequent and more severe with ABVD (grade ≥3: 3% ABVD vs <1% A+AVD).

There were 28 deaths in the A+AVD group and 39 in the ABVD group; interim 2-year OS was 96.6% for the A+AVD group (95% CI, 94.8-97.7) and 94.9% for the ABVD group (95% CI, 92.9-96.4).

A+AVD had superior efficacy to that of ABVD in the treatment of patients with advanced-stage HL, with a 4.9 percentage–point lower combined risk of progression, death, or non-complete response at 2 years, the results of the study showed. "This establishes A+AVD as a new frontline option for patients with advanced-stage HL," Connors concluded. ◆

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Balancing Hospice Utilization With the Need for Transfusion in Leukemia

Surabhi Dangi-Garimella, PhD

IS TRANSFUSION DEPENDENCE A barrier to hospice utilization among older patients with leukemia who are enrolled in Medicare? This was the query posed by a collaborative study among researchers at Brown University, Rhode Island Hospital, and Duke Cancer Institute, presented during an Outcomes Research session at the 59th Annual Meeting and Exposition of the American Society of Hematology.[1]

Patients with blood cancers use palliative and hospice services at end of life (EOL) less frequently than those with solid tumors. Previous studies have suggested that transfusion dependence (TD) may be a barrier to hospice enrollment, as life-extending transfusion support may not be allowed by hospice organizations. A 2015 study in *Cancer*,[2] which evaluated healthcare utilization and EOL use in older patients with acute myeloid leukemia, found that hospice services were rarely utilized in their study cohort. The need for frequent blood product support in these patients may be a significant factor, the authors wrote.

A more recent study, which conducted a survey among US hematologic oncologists to gather their perspective on the utility of hospice care for patients with blood cancers, found that despite the value of hospice care, lack of adequate services prevented them from making hospice referrals. More than half of the survey respondents said that they were more likely to refer their patients to hospice services if red cell/platelet transfusions were available.[3]

Presenting the results of the current study was Thomas W. LeBlanc, MD, medical oncologist and palliative care physician with the Duke Cancer Institute, Durham, North Carolina.

"Most hospices do not allow transfusion support," LeBlanc said, adding that while TD has been noted as a barrier for hospice use, it has not been well studied in the context of leukemia. LeBlanc explained that the lack of transfusion support in hospices is a practical matter, where per diem reimbursement by CMS is small. "Therefore, we sought to evaluate the association between TD and outcomes at EOL among Medicare beneficiaries with acute and chronic leukemias."

The study used claims information from the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare database to identify Medicare beneficiaries 65 years and older with acute (myeloid or lymphoblastic) and chronic (lymphocytic, myeloid, or myelonomocytic) leukemias, diagnosed between 1996 and 2011 and who died between 2001 and 2011, at least 30 days from diagnosis. The longer timeframe, LeBlanc said, would account for the expected longer lifespan with chronic leukemias. TD was defined as at least 2 transfusions—at least 5 days apart, inpatient or outpatient—within 30 days before death or hospice enrollment.

Primary endpoints included use of hospice services at EOL and duration of hospice stay. Secondary endpoints included National Quality Forum performance measures for palliative care:

- Intensive care unit use within 30 days of death
- Chemotherapy in the last 14 days of life
- Hospice enrollment less than 3 days before death
- Hospice enrollment via outpatient referral

Cost of care at EOL was approximated as inflation-adjusted Medicare spending within 30 days before death.

Of the original 35,672 patients who were returned following a SEER-Medicare query, patients with incomplete Medicare claims as well as patients who enrolled in hospice prior to diagnosis were excluded. From the remaining pool of patients with complete Medicare data, patients with less than 30 days of survival were eliminated. This left the authors with a cohort of 21,076 eligible patients (median age, 79 years; 44% women; 46% acute leukemias), 20% of whom were TD before death/hospice enrollment.

TD patients were significantly younger, more often male, and more often had acute leukemia. Use of hospice at EOL increased from 35% in 2001 to 49% in 2011 (P <.0001), and it was higher among patients with TD than those without it (47% versus 43%, respectively; P <.0001). There was a reciprocal trend toward fewer inpatient deaths and chemotherapy use at EOL. Median time on hospice was 9 days, and it was significantly shorter for TD patients (6 vs 11 days; P <.0001), who were also more likely to receive hospice services for less than 3 days (27% vs 19%; P <.0001).

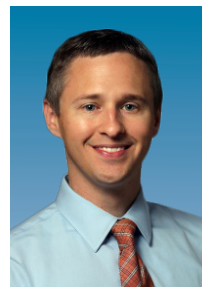
There was no significant difference in death in the inpatient setting between TD (46%) and non-TD (43%) patients. Chemotherapy use in the last 14 days of life was slightly higher in the TD patients (14% versus 11%).

LeBlanc said that TD was associated with a slightly higher likelihood of hospice enrollment (relative risk [RR], 1.07; 95% CI, 1.03-1.11), but also with a 52% shorter time on hospice (RR, 0.48; 95% CI, 0.44-0.54). TD was also associated with less frequent outpatient hospice referral in chronic leukemia (RR, 0.73; 95% CI, 0.65-0.82) but not in acute leukemia (RR, 0.96; 95% CI, 0.90-1.03).

Importantly, hospice enrollees had a lower likelihood of inpatient death (3% vs 75%) and chemotherapy use in the last 14 days of life (5% vs 16%), and they had lower median Medicare spending at EOL ($7662 vs $17,783) than non-enrollees.

LeBlanc concluded that that while hospice use has increased in patients with leukemias, the results of their study associate TD with significantly shorter hospice length of stay, which could implicate it as a barrier to hospice enrollment.

He warned, however, that the use of claims-based data in their study prevented them from adjusting for any marker of disease severity. Additionally, the findings may not hold true for non-Medicare patient populations, including younger patients or those on managed-care plans. ◆



LEBLANC

Thomas W. LeBlanc, MD, is a medical oncology and palliative care physician with the Duke Cancer Institute, Durham, North Carolina.

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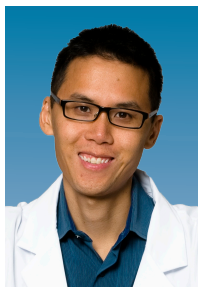
QUALITY OF LIFE

Using Time Spent at Home to Measure End-of-Life Care Quality

Jaime Rosenberg



CHEUNG

Matthew Cheung, MD, MS, FRCP, is an associate scientist, Sunnybrook Health Sciences Center, Toronto, Ontario.

THERE ARE SEVERAL DEMOGRAPHIC features of patients with hematologic malignancies that affect their likelihood of dying at home, suggesting a crucial role for access to caregiver support, according to an abstract presented at the 59th Annual Meeting of the American Society of Hematology in Atlanta, Georgia.

"Despite advances in the management of patients with hematologic malignancies, a significant proportion of patients will still die of their disease," the study authors wrote.

Existing quality indicators at the end of life (EOL) focus on whether patients receive aggressive interventions such as chemotherapy during the last days of life. However, many patients and caregivers have put emphasis on the importance of time spent at home as a quality measure for EOL care.

Using a population-based health system administration database from Ontario, Canada, the authors identified 6792 adult patients who died of a hematologic malignancy between January 2005 and December 2013. The primary outcome of "days at home" in a patient's last 6 months of life was defined as 180 days minus the number of days in an acute care facility.

Patients who received palliative care consultation prior to the last 6 months of life were more likely to spend time at home than patients who had not been seen by a palliative care specialist.

The authors also accounted for patient variables, such as comorbidities identified by a mortality risk score, and system level variables, such as palliative care consultation prior to the last 6 months of life, that predicted the number of days at home and determined trends over time.

The patients' median age was 72 at the time of death, and 58% of the patients were male. The median number of days at home during the last 6 months of life was 156 days; 81% of the patients spent more than 120 days at home (FIGURE).

Patients who were older spent more time at home than younger patients, and women spent less time at home than men. A possible explanation for this is that women typically live longer than men, and when women get sick, their spouses have often already died or can't provide care because they are too frail, said lead author Matthew Cheung, MD, MS, FRCP, associate scientist, Sunnybrook Health Sciences Center in an interview with *The American Journal of Managed Care®*.

In addition, Cheung said, patients getting at least 2 or more transfusions were spending much less time at home than those who did not require transfusions, which could signal being unable to access transfusions while at home or that the patients are sicker. or the patients are sicker.

Patients who received palliative care consultation prior to the last 6 months of life were more likely to spend time at home than patients who had not been seen by a palliative care specialist (OR 1.34; CI, 1.20-1.49; $P< .0001$). Meanwhile, patients with more comorbidities were less likely to spend time at home (OR 0.96; CI, 0.96-0.97; $P< .0001$).

"We see that there may be a few targetable patient characteristics that can be identified to help us better help patients spend time at home," said Cheung. "Patients with comorbidities, women, and patients who are younger spend less time at home, so we can target these patients." ◆

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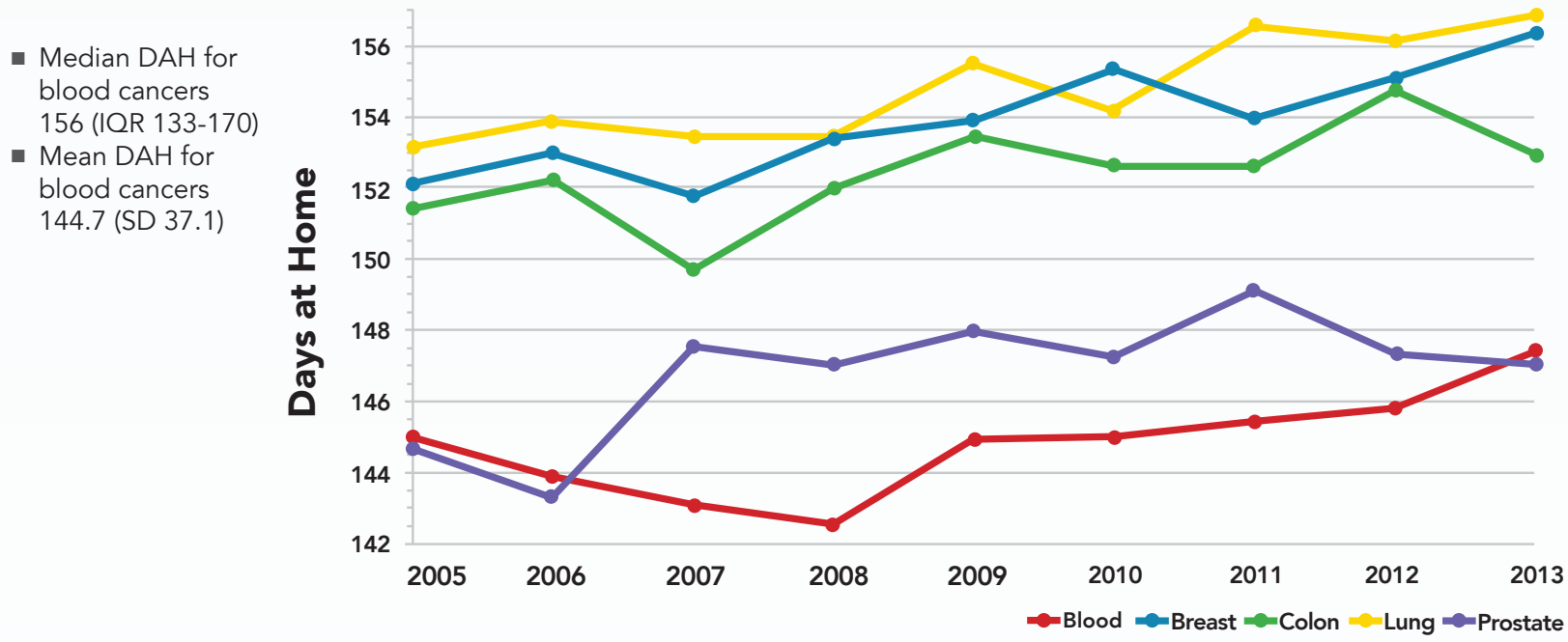
FIGURE. Mean Days at Home in Last 180 Days of Life for Major Cancers



DAH indicates days at home; IQR, interquartile range; SD, standard deviation.

Source: Cheung M, Andersen S, Earle CC, Croxford R, Singh S. Days spent at home in the last 6 months of life: a potential patient-determined quality indicator for patients with hematologic malignancies at the end of life. Presented at the 59th Annual Meeting of the American Society of Hematology; December 9-12, 2017; Atlanta, Georgia. Abstract 281.

Patients With AL Amyloidosis From Lower Socioeconomic Status Report Lower Quality of Life

Jaime Rosenberg

PATIENTS WITH AMYLOID LIGHT CHAIN (AL) AMYLOIDOSIS from lower socioeconomic status (SES) groups had poorer health-related quality of life (HRQoL) when compared to patients with more education and/or professional/managerial positions, according to an abstract presented at the 59th Annual Meeting of the American Society of Hematology in Atlanta, Georgia.

"SES can affect HRQoL through a variety of mechanisms, including poor access to healthcare, physical and mental comorbidities, low levels of health literacy or health activation, and consequent negative health behaviors," wrote the study authors.

The cross-sectional, observational study looked at 1289 patients with AL amyloidosis evaluated between 1994 and 2014 at the amyloidosis Center at Boston University. Participants completed the SF-36v1 Health Surveys, within 7 days of their initial evaluation, which assessed HRQoL in relation to 8 domains and 2 component measures:

- Physical functioning (PF)
- Role limitations due to physical health problems (RP)
- Bodily pain (BP)
- General health (GH)
- Vitality (VT)
- Social functioning (SF)
- Role limitation due to emotional health problems (RE)
- Mental health (MH)
- Physical (PCS) and mental component summaries (MCS)

Participant SES was determined based upon occupation type and educational attainment. Authors used regression models including each SF-36v1 domain or summary score as a dependent variable to determine if there was a link between SES and HRQoL. The association was determined independent of other characteristics such as type of organ involvement, multiorgan involvement, eligibility for stem cell transplantation, and time since diagnosis.

The models produced results showing patients with less years of education reporting worse HRQoL impairment compared to patients with more education. Differences by educational attainment (with the exception of GH, MH, and MCS) all exceeded a threshold of 1 minimally important difference (MID).

Using occupation at the independent variable for SES, scores also differed drastically by occupation. Patients in other (non-professional/managerial) occupations reported statistically ($P < .05$ for all) and clinically (exceeding 1 MID) substantial deficits on all SF-36v1 scores.

Patients on disability presented significantly worse SF-36v1 scores ($P < .05$ for all), and deficits exceeded 1 MID for all scores. For PF, VT, and PCS, the differences surpassed 2 MIDS. Patients who were retired conveyed significant deficits for PF and RP ($P < .05$ for both).

"Outreach efforts designed to increase the understanding of the disease among community-based clinicians should highlight the additional HRQoL burden and potential need for more comprehensive care among patients with SES groups," the authors concluded. ◆

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The Effects of Myeloproliferative Neoplasm Symptoms on Quality of Life

Jaime Rosenberg

A SECONDARY ANALYSIS PRESENTED at the 59th Annual Meeting of the American Society of Hematology in Atlanta, Georgia, found that all individual symptoms of myeloproliferative neoplasms (MPNs) correlate with quality of life (QoL).

"Patients with MPNs are faced with high disease-related symptom burden and QoL decrements," the authors wrote.

Previous study results have shown that symptom burden measured from the MPN Symptom Assessment Form (MPN-SAF) Total Symptom Score has a strong correlation with QoL measured by the Global Health Status/QoL (GHS/QoL) scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). However, according to the authors, an analysis of predictors of QoL in this population has not been performed.

The authors used data from the previously enrolled cohort of 1422 patients with MPNs who completed a MPN-SAF and EORTC QLQ-C30. The association between individual symptoms and QoL was assessed by the GHS/QoL scale of the EORTC QLQ-C30.

Two sets of summary measures were then established: the presence of at least 1 symptom with a score of 1 or higher, presence of at least 1 symptom with a score of 2 or higher, and so on up to a score of 10; and total number of symptoms with a score of 1 or higher, total number of symptoms with a score of 2 or higher, and so on up to a score of 10.

The median correlation between individual symptoms and QoL was –0.36 (range –0.23, –0.54, all $P < .001$). The symptoms that yielded the strongest correlations were inactivity (–0.54, $P < .001$), fatigue (–0.48, $P < .001$), depression (–0.48, $P < .001$), and dizziness (-0.44, $P < .001$). The symptoms that yielded the weakest correlations were fever (-0.23, $P < .001$), cough (-0.27, $P < .001$), night sweats (-0.27, $P < .001$), and sexual desire/function (–0.30, $P < .001$).

While study findings suggest that all individual symptoms correlate to a certain extent with quality of life, inactivity was the most correlated; having 1 severe symptom and having multiple symptoms of moderate intensity were meaningfully correlated with quality-of-life reduction.

Results also showed that the median correlation between QoL and the presence of at least 1 symptom with a score of 1-10 was -0.36 (range -0.20, -0.40). The strongest correlations were seen from the presence of: at least 1 symptom at or above a score of 6 (–0.40, $P < .001$), a score of 7 (–0.39, $P < .001$), and a score of 8 (–0.38, $P < .001$). The weakest correlations were seen from a score of 1 (–0.20, $P < .001$), a score of 2 (–0.27, $P < .001$), and a score of 10 (–0.29, $P < .001$).

Although study findings suggest that all individual symptoms correlate to a certain extent with QoL, inactivity was the most correlated; having 1 severe symptom and having multiple symptoms of moderate intensity were meaningfully correlated with QoL reduction.

"The symptom burden experience is variable and undoubtedly bears heavily on quality of life among patients with MPNs as supported by these results," the authors concluded. ◆

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Significant Economic Burden Associated With Various AML Treatment Episodes

Jaime Rosenberg

THERE IS A SUBSTANTIAL economic burden associated with multiple acute myeloid leukemia (AML) treatment episodes, according to an analysis presented at the 59th Annual Meeting of the American Society of Hematology in Atlanta, Georgia.

AML is estimated to affect over 20,000 people in the United States in 2017, according to the authors of the analysis.

"Detailed real-world cost estimates and comparisons of key AML treatment episodes such as high-intensity chemotherapy (HIC), low-intensity chemotherapy (LIC), hematopoietic stem cell transplant (HSCT) and relapsed-refractory (R/R) patient episodes in the US commercially insured population are scarce and difficult to assemble," wrote the authors.

The authors examined a large US healthcare claims database, PharMetrics Plus, and linked charge detail master (CDM) hospital data to identify patients with an AML diagnosis between January 1, 2008, and March 31, 2016. Patients with 2 or more outpatient claims or 1 or more inpatient claims were included.

Participants were required to have continuous health plan enrollment for ≥ 6 months pre and ≥ 3 months post the first diagnosis date. The authors evaluated:

- HIC induction: evidence of inpatient high dose cytarabine+anthracycline use within 3 months of diagnosis
- HIC consolidation: evidence of cytarabine +/- anthracycline use within 2 months following prior HIC
- LIC: evidence of low-intensity cytarabine, anthracycline, 5-azacytidine, decitabine, clofarabine, hydroxyurea or gemtuzumab ozogamicin in the outpatient setting within 3 months of diagnosis
- HSCT: transplant specific diagnosis/procedure codes
- R/R patients: record of an ICD-9 diagnosis code (205.02) for relapsed AML after a prior treatment of HIC, LIC, or HSCT

The study consisted of 1542 HIC induction, 591 consolidation, 628 LIC, 1000 HSCT, and 119 R/R patients. The total mean (SD) episode cost was the highest among HSCT patients, costing $329,621; followed by HIC induction cost of $198,528; R/R cost of $145,634; and HIC consolidation cost of $73,304. The lowest episode cost was associated with LIC ($53,081).

Other findings included:

- Hospitalization costs accounted for $244,801 for HSCT.
- All HIC induction required hospitalization and accounted for most of the HIC cost, with $2843 attributed to physician's office visits and $2868 attributed to outpatient pharmacy.
- Hospitalization occurred in 74.8% of R/R patients at a cost of $101,420; physician's office visits costs were $3340, and outpatient pharmacy costs were $6108.
- Although LIC patients had a relatively low hospitalization rate (35.8%), hospitalization was a major cost contributor at $17,764.

"This resource utilization and direct healthcare cost analysis establishes a substantial economic burden associated with various AML treatment episodes, notable during the HIC induction, HSCT and R/R episodes in the US," the authors concluded. "Hospitalization is a major cost driver across all episodes. New therapeutic strategies associated with less economic burden are needed." ◆

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Financial Incentives May Lead to Overuse of Rituximab Maintenance

Kelly Davio

RECEIVING LYMPHOMA CARE IN the community-based setting is associated with guideline-discordant use of rituximab, according to investigators.[1] Scott Huntington, MD, MPH, presented his research team's findings December 9 at the 59th American Society of Hematology Annual Meeting and Exposition in Atlanta, Georgia.

Maintenance rituximab monotherapy has been shown to improve progression-free survival in some lymphoma settings, but current guidelines support just 2 years of rituximab maintenance. Data from studies in other disease states suggest that financial incentives may influence the use of infused therapies in US patients, and Huntington and colleagues sought to determine whether community providers (who may have financial incentives to provide rituximab beyond guideline-based time periods) were more likely than hospital-employed providers to prescribe extended maintenance rituximab.

HUNTINGTON

Using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, the researchers identified older adults who were diagnosed with B-cell non-Hodgkin lymphoma between 2004 and 2011 and had at least 1 claim for rituximab through 2013. Patients were included in the study if they had more than 7 months of claims without a 200-day gap.

The number of rituximab monotherapy claims and the duration of maintenance therapy were calculated for each patient until the receipt of chemotherapy, a 200-day gap in rituximab claims, or death, and the site of administration was classified as community or hospital-outpatient (as identified on Medicare claims). A logistic regression model was used to assess the association between care setting and prolonged use of rituximab monotherapy.

The investigators identified 2620 patients with 2 years of available follow-up after initiation of rituximab maintenance; 75.1% received their therapy in a community setting. The median number of maintenance doses received was 9 (range, 1-103), and the median duration was 14 months (range, 0-92), with 261 (10.0%) patients receiving uninterrupted rituximab maintenance for more than 2 years.

Patients in the community setting were more likely to receive rituximab maintenance for longer than the guideline-recommended period; 11% of patients in the community setting versus 6.9% in the hospital setting received it for more than 2 years. Furthermore, treatment in a community setting was significantly associated with a patient's receipt of more than 2 years of maintenance (adjusted odds ratio [OR], 1.56; 95% CI, 1.10-2.20; $P = .012$), as well as with receipt of more than 12 doses of rituximab as monotherapy (adjusted OR = 2.01; 95% CI, 1.63-2.48; $P < .001$).

The authors concluded that receiving lymphoma care in the community setting is associated with guideline-discordant use of rituximab, with financial incentives for using anticancer therapies possibly contributing to the overuse. "Providers practicing in the physician office setting are more likely to derive income directly from chemotherapy administration compared [with] hospital-employed physicians," Huntington told The Center for Biosimilars® in an e-mail. "Prior research suggests physicians in community settings are more responsive to reimbursement changes in their choice of chemotherapy regimens compared with hospital-employed providers."

While it is not known whether changes to reimbursement translate into treatment that is discordant with guidelines, Huntington said that "financial incentives likely contribute to overutilization during rituximab maintenance, and future studies should consider treatment setting when evaluating cancer-therapy utilization. Our findings support ongoing efforts to minimize financial incentives tied to chemotherapy administration to better align payment with high quality care." ◆

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Kymriah More Cost-Effective in Pediatric Patients With Acute Lymphoblastic Lymphoma

Jaime Rosenberg

ACCORDING TO RESULTS FROM 2 studies presented at the 59th Annual Meeting & Exposition of the American Society of Hematology in Atlanta, Georgia, CTL019, sold as Kymriah by Novartis, shows promising potential in providing significant benefit and cost-effectiveness for pediatric and young-adult patients with B-cell acute lymphoblastic leukemia (ALL).

Studying populations in the United States and the United Kingdom, investigators assessed the efficacy of CTL019 (tisagenlecleucel), a chimeric antigen receptor T-cell therapy, in pediatric and young-adult patients with relapsed or refractory (r/r) ALL.

Currently, treatments for r/r pediatric ALL include: clofarabine monotherapy (Clo-M), clofarabine combination therapy (Clo-C), blinatumomab (Blin), other salvage chemotherapies (SCs), and allogeneic stem cell transplant (SCT). SCT is considered the only potentially curative option, according to the authors of the US study.[1]

"However, less than 50% of patients with multiple relapses achieve complete remission from existing treatments, and even fewer are eligible for and ultimately receive SCT," the authors wrote.

The authors developed a partitioned survival model to assess the incremental cost-effectiveness of CTL019 compared with Clo-M, Clo-C, Blin, SC, and second SCT over a 20-year period. The model included 3 health states: event-free survival, progressive disease, and death. Incremental life-years (LYs), incremental quality-adjusted life-years (QALYs), and incremental cost per QALY gained were estimated comparing CTL019 with each comparator.

The results showed that over the 20-year span, treatment with CTL019 provided an increase of 4.62, 3.79, 3.68, 2.08, and 2.05 in discounted LYs and an increase of 4.29, 3.64, 2.23, and 2.31 in discounted QALYs relative to Clo-M, Clo-C, Blin, SC, and SCT, respectively. Using incremental cost-effectiveness ratios (willingness-to-pay thresholds) from $100,000/QALY to $300,000/QALY, the value-based prices for treatment with CTL019 ranged from $488,470 to $1,364,525.

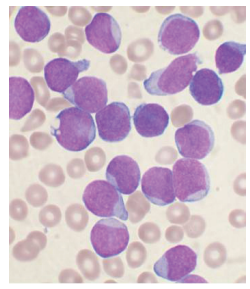
The UK National Institute for Health and Care Excellence (NICE) recently conducted a cost-effectiveness analysis that modeled the benefits of CTL019 relative to the costs using early trial data.

The authors of the UK study[2] expanded on the NICE model to quantify the economic value compared with clofarabine by assessing the economic value of the incremental QALYs gained for 10 incident cohorts including 380 patients. The authors calculated the economic value of each QALY gained as £50,000 ($67,000 US). Costs for other factors such as conditioning, hospitalizations, adverse events, and hematopoietic stem cell transplantation and follow-up costs were also included.

Building on the NICE report, the authors calculated the patients' expected productivity using nationally representative data and calculated the consumer surplus accruing to patients from the use of CTL019.

Results showed that patients gained 3294 QALYs from CTL019 relative to clofarabine, which translated to £164,690,866 ($220,950,348 US) of total value; £49,525,920 ($66,444,299 US) was attributable to added patient productivity from employment gains. Using the 3 prices considered by NICE (£250,000, £356,100, and £528,600 [$335,401, $477,746, and $709,173 US]), the consumer surplus accruing to patients was £91,847,131, £57,142,661, and £719,276 ($123,222,714, $76,662,969, and $964,985), respectively. This amounts to an average of £280,799, £174,699, and £2199 ($376,721, $234,377, and $2950 US) of consumer surplus accruing to each patient, according to the authors.

"In our model, it produced very large numbers for the value of extended survival and improved quality of life for treating kids and young adults who, without these therapies, have a very high mortality risk," said Julia Snider, PhD, Precision Health Economics, in an interview with *The American Journal of Managed Care®*. "This has potential to treat them and allow them to grow up, get jobs, and become functioning members of society." ◆



Bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia.

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New Data Support Using Tbo-Filgrastim in Pediatric Patients

Kelly Davio

IN RESEARCH PRESENTED AT the 59th American Society of Hematology Annual (ASH) Meeting and Exposition in Atlanta, Georgia, Noah Federman, MD, evaluated the safety and efficacy of subcutaneous tbo-filgrastim (Granix) in pediatric patients undergoing chemotherapy for solid tumors.[1]

Chemotherapy-induced neutropenia, a common adverse event (AE), can limit optimal dosing and treatment. Tbo-filgrastim, a nonglycosylated recombinant methionyl human granulocyte colony-stimulating growth factor (G-CSF), is indicated to reduce the duration of severe neutropenia in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer therapy associated with clinically significant incidence of febrile neutropenia. Tbo-filgrastim is not technically a biosimilar of filgrastim (Neupogen); it was approved prior to the establishment of a biosimilar approval pathway in the United States.[2] However, the 2 drugs do not differ significantly in terms of pharmacokinetic (PK) parameters, safety, or efficacy.

FEDERMAN

This phase 2, multicenter, open-label study investigated the safety, tolerability, PK, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim in patients aged 1 month to 16 years who had solid tumors without bone marrow involvement and had received at least 1 cycle of myelosuppressive chemotherapy.

Patients (n = 50) were given a subcutaneous dose of tbo-filgrastim at 5mcg per kilogram of body weight once daily. Tbo-filgrastim administration was started at approximately 24 hours after the end of the last chemotherapy treatment, and daily dosing continued until the expected neutrophil nadir has passed and neutrophil count had recovered, but not for more than 14 days.

The most common cancers for which the 2 infants (aged 1 month to 2 years), 30 children (2 to 12 years), and 18 adolescents (12 to 16 years) were being treated were rhabdomyosarcoma (14%), neuroblastoma (14%), Ewing tumors (12%), and osteosarcoma (12%). The mean number of doses of tbo-filgrastim administered was 9.2 in children and 7.3 in adolescents. One infant patient received 12 doses and the other, 14.

"As we all know, chemotherapy-induced neutropenia is a common complication from chemotherapy [that] may lead to prolonged hospitalization, increased morbidity, and limitation of optimal dosing of chemotherapy and treatment of cancer."

—Noah Federman, MD

Serious treatment-emergent AEs were reported in 24% of patients, with febrile neutropenia (12%), anemia (8%), thrombocytopenia (8%), increased alanine aminotransferase (6%), and increased aspartate aminotransferase (6%) being the most commonly reported. Nine patients experienced treatment-related AEs, most commonly musculoskeletal and connective tissue disorders (8%) of grade 1 severity. Two patients had increases in liver function enzymes that the investigator considered to be related to tbo-filgrastim and chemotherapy; no clinical symptoms were observed in these events, and both resolved by the end of the study. No deaths or study withdrawal occurred during the study period.

PK parameters of exposure were comparable between age groups. The incidence of severe neutropenia was 52%, with a mean duration of 1.8 days. The incidence of febrile neutropenia was 26%. Immunogenicity assessments found that none of the patients had developed anti-drug antibodies to tbo-filgrastim.

RESULTS ARE PROMISING FOR USE OF TBO-FILGRASTIM IN PEDIATRIC PATIENTS.

The researchers concluded that a daily dose of tbo-filgrastim at 5 mcg per kg of body weight administered to pediatric patients with solid tumors without bone marrow involvement demonstrated a safety profile consistent with that of adult patients, and no immunogenic response was observed in this population.

"We are very excited to present the results of the first study of tbo-filgrastim in children," Federman told The Center for Biosimilars® in an e-mail. "As we all know, chemotherapy-induced neutropenia is a common complication from chemotherapy [that] may lead to prolonged hospitalization, increased morbidity, and limitation of optimal dosing of chemotherapy and treatment of cancer.…G-CSF, while standard of care, is quite expensive, and there is a need for additional agents to expand access."

At the ASH meeting, Federman said, "We will be sharing what I believe is quite compelling data to support the use of tbo-filgrastim in children after receiving myelosuppressive chemotherapy and applaud this momentous global collaborative effort in an orphan disease population with few approved medications." ◆

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BIOSIMILARS UPDATE

Study Results Show Low Incidence of Immunogenicity With Tbo-Filgrastim

Kelly Davio

NEUTROPENIA, A PRIMARY CAUSE of delays, interruptions, and dose reduction to chemotherapy, can compromise both patient survival and complete response rates. Granulocyte colony-stimulating factors (G-CSFs), including tbo-filgrastim (Granix), can reduce the incidence, duration, and severity of febrile neutropenia in patients receiving chemotherapy. However, serious immune reactions can be caused by drugs like tbo-filgrastim (a follow-on filgrastim product approved before the United States instituted a regulatory pathway for the approval of biosimilar products under the Biologics Price Competition and Innovation Act).

The production of antidrug antibodies (ADAs) can have negative consequences for patients, including such reactions as anaphylaxis, reduced efficacy, and neutralization of endogenous counterparts by cross-reactive neutralizing antibodies. A new study, conducted by Linglong Zou, PhD, and colleagues, evaluates the immunogenicity of tbo-filgrastim in patients receiving chemotherapy for solid and hematologic malignancies.[1] The data were presented at the 59th American Society of Hematology Annual Meeting and Exposition in Atlanta, Georgia.

Zou and his team collected blood samples during 3 different phase 3 clinical studies that compared the efficacy and safety of tbo-filgrastim with filgrastim and/or placebo, administered 1 day after chemotherapy for a duration of 5 to 14 days. The team implemented a 3-tier approach—screening, confirmation, and a titer assay—to evaluate binding ADAs for tbo-filgrastim using a validated homogeneous enzyme-linked immunosorbent assay. Neutralizing activity was assessed for confirmed-positive ADA test samples using a validated cell-based proliferation assay. Clinical measures were examined for all patients who had confirmed ADAs to assess a possible correlation between ADAs and the potential clinical impact of immunogenicity.

In total, 436 patients diagnosed with cancer who had received tbo-filgrastim were assessed for immunogenicity of the follow-on filgrastim product. These patients had breast cancer (n = 213), lung cancer (n = 160), or non-Hodgkin's lymphoma (n = 63).

Only 3 patients with breast cancer developed ADAs at a low titer, and none of the samples showed cross-reactivity to endogenous G-CSF or neutralizing antibody activity. Three patients with lung cancer developed ADAs at a low titer, but none of the ADA-positive samples cross-reacted with endogenous G-CSF, and 1 predose sample showed neutralizing antibody activity in cycle 1 prior to tbo-filgrastim treatment. Among the patients with non-Hodgkin's lymphoma, 1 developed ADAs at a titer too low to be determined. No cross-reactivity or neutralizing antibody activity was associated with this patient's blood sample. Overall, immunogenicity incidence was 1.6% among all the patients tested, and none of those with positive ADA samples showed evidence of hypersensitivity, anaphylaxis, or a loss of treatment efficacy.

The researchers concluded that the incidence of immunogenicity or treatment-emergent ADAs in patients who were receiving chemotherapy and tbo-filgrastim was low across the 3 cancer populations tested and all positive samples had low-titer ADAs. None of the positive samples had cross-reactive ADAs to endogenous G-CSF, and none of the patients who had positive ADA samples had clinically relevant immunogenicity-related symptoms during the study period. ◆

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2 Studies Highlight Biosimilar G-CSFs

Samantha DiGrande

TWO STUDIES PRESENTED AT the 59th American Society of Hematology Annual Meeting and Exposition in Atlanta, Georgia, highlight biosimilar granulocyte-colony stimulating factor (G-CSF) therapies.

Biosimilar Filgrastim Saves Costs

The savings generated by using biosimilars can be reallocated to provide other treatments, including expensive and recently approved novel therapies, according to study results presented by Sanjeev Balu, PhD. The study examines expanded access to the drug obinutuzumab (Gazyva) made possible on a budget-neutral basis through savings obtained from using biosimilar filgrastim-sndz (Zarxio).[1]

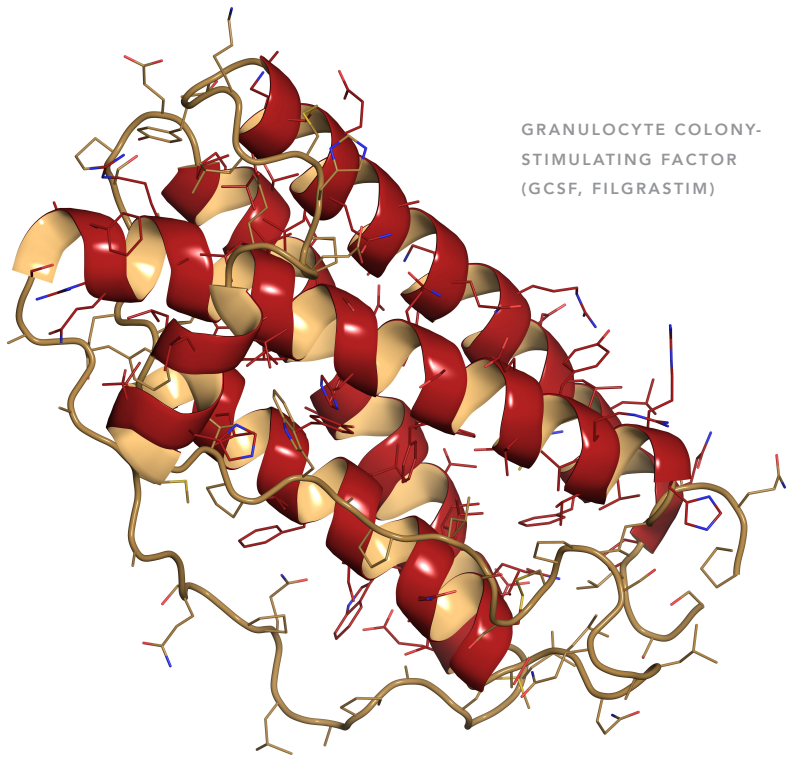
The investigators estimated the potential costs saved by converting febrile neutropenia prophylaxis from reference filgrastim (Neupogen) or pegfilgrastim (Neulasta) to the biosimilar filgrastim, and then simulated a hypothetical reallocation of those savings to therapeutic care with obinutuzumab (a humanized anti-CD20 monoclonal antibody approved in 2016 for relapsed or refractory follicular lymphoma).

Assuming therapeutic similarity of filgrastim, pegfilgrastim, and biosimilar filgrastim, a simulation analysis was performed using the average selling price cost for 1 patient for 1 chemotherapy cycle with 5, 7, 11, and 14 days of prophylaxis. This study was performed with a 20,000-patient panel.

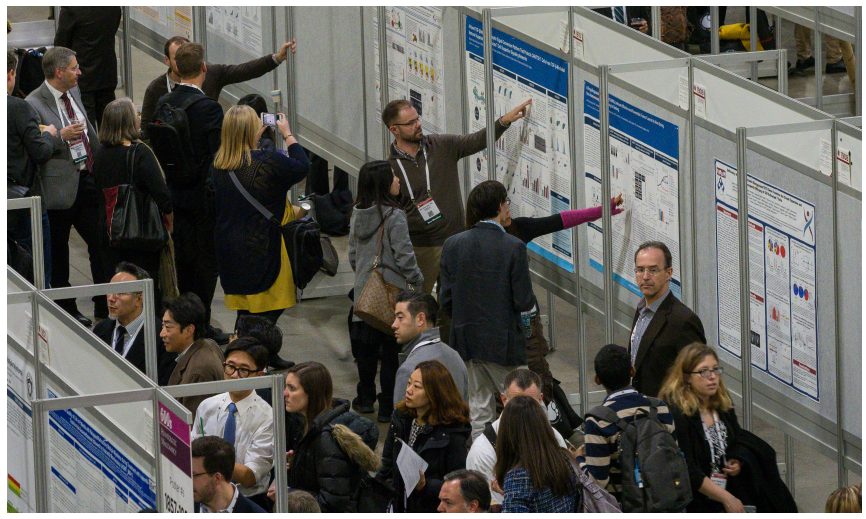
Per-cycle cost savings from utilizing biosimilar filgrastim over filgrastim was estimated at $327 (5-day prophylaxis), $457 (7-day), $719 (11-day), and $915 (14-day). For 20,000 patients, conversion from filgrastim to biosimilar filgrastim was estimated to yield savings of $6,540,000 (5-day prophylaxis); $9,156,000 (7-day); $14,388,000 (11-day); and $18,312,000 (14-day). The savings would provide expanded access to obinutuzumab treatment to 60, 85, 133, and 169 patients, respectively.

Conversion-related savings relative to pegfilgrastim decline as daily injections increase. For 20,000 patients, conversion from pegfilgrastim to the biosimilar filgrastim would yield savings of $55,893,600 (5-day prophylaxis); $47,177,600 (7-day), $29,745,600 (11-day); and $16,671,600 (14-day), the authors found. This would expand access to obinutuzumab treatment to 516, 435, 275, and 154 patients, respectively.

The results show that converting from reference filgrastim and pegfilgrastim to biosimilar filgrastim yields significant savings, especially when converting from pegfilgrastim. Conversion to biosimilar growth factors for prophylaxis of febrile neutropenia in large payer panels can create substantial savings that enable more patients with hematological malignancies to be treated without additional cost to payers, according to the authors.



GRANULOCYTE COLONY-STIMULATING FACTOR (GCSF, FILGRASTIM)



ATTENDEES MINGLE DURING THE POSTER HALL WELCOME RECEPTION AT THE 59TH AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING AND EXPOSITION.

Cinfa Biotech's Pegfilgrastim Candidate Has Similar PD, Immunogenicity to Neulasta

Cinfa Biotech's proposed pegfilgrastim biosimilar, B12019, has similar pharmacodynamics (PD) and immunogenicity to the reference Neulasta, according to a research team led by Karsten Roth, PhD.[2]

B12019 is being developed as a biosimilar to Neulasta, a long-acting form of recombinant human granulocyte-colony stimulating factor (G-CSF) filgrastim for the prevention of chemotherapy-induced neutropenia. Cinfa's clinical development program, based on scientific advice from the European Medicines Agency, consists of 2 clinical studies conducted to confirm the biosimilarity to the European Union–authorized reference product as established by analytical, functional, and preclinical data. This study investigates the immunogenicity and pharmacodynamic comparability of the biosimilar and reference at a dose of 3 mg.

The 3-mg dose was selected because, compared with clinical dose of 3 mg, it is more sensitive for detecting potential differences in PD between the biosimilar and the reference. This study was designed as a multiple-dose, randomized, double-blind, 3-period, 2-sequence cross-over study in 96 healthy individuals.

A hierarchical antidrug-antibody (ADA) test strategy with highly sensitive screening assay followed by 4 parallel epitope-specific, confirmatory assays was established. Primary study end points were area under the effect curve ($AUEC_{0\text{-last}}$) of the absolute neutrophil count for PD after crossover and the ADA rate for immunogenicity after repeat dosing.

The number of ADA-positive subjects was very low for both the B12019 and Neulasta groups. No imbalance was observed between either drug after repeat doses. Neither anti-filgrastim nor neutralizing antibodies were detected for B12019 or Neulasta. The model-based PD comparison included 82 subjects; comparability was demonstrated, and there were no clinically meaningful differences observed in the safety profile for B12019 and Neulasta.

This study of the prospective biosimilar to the reference pegfilgrastim confirmed PD comparability with the reference product at a sensitive dose of 3 mg, and the researchers concluded that the study confirmed biosimilarity of the proposed biosimilar to the reference. ◆

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Presenters Share New Data on Rituximab Biosimilars Approved in European Union, Argentina

Samantha DiGrande

ALTHOUGH NO RITUXIMAB BIOSIMILARS have been approved in the United States to date, experience with rituximab therapies approved in other regulatory areas adds to the body of evidence concerning these products' safety and efficacy.

European Union–Approved Biosimilar Safe for Rapid Infusion

Raakhee Shah, MPharm, and colleagues presented study results demonstrating that patients can be switched from reference rituximab (MabThera) to biosimilar rituximab (Truxima) without reverting to slower infusion rates.[1]

Rituximab is a monoclonal antibody approved in the European Union and United States to treat non-Hodgkin's lymphoma and chronic lymphocytic leukemia, as well as other indications, and can be associated with infusion-related reactions (IRRs). The incidence is greatest with the first infusion and decreases significantly with subsequent infusions.

To reduce the risk of IRRs, manufacturers recommend that the first dose be gradually increased every 30 minutes in increments of 50 mg per hour to a maximum rate of 400 mg per hour. For subsequent infusions, the dose is gradually increased every 30 minutes in increments of 100 mg per hour, known as standard subsequent rate infusion. That means a typical rituximab infusion can take 4 to 6 hours.

If the first infusion is well tolerated, it has become common practice to administer subsequent doses as a "rapid infusion" over 90 minutes, with 20% of the dose given over the first 30 minutes and the remaining 80% over the following 60 minutes.

This study aimed to assess the safety of rapid infusion of biosimilar rituximab by reviewing infusion-related adverse events (AEs) that fall into 3 categories:

- Patients switching from the reference product, MabThera, to the biosimilar (n = 78)
- Patients with previous exposure to the reference product but who received their last dose over 6 months prior (n = 6)
- Rituximab-naïve patients (n = 58)

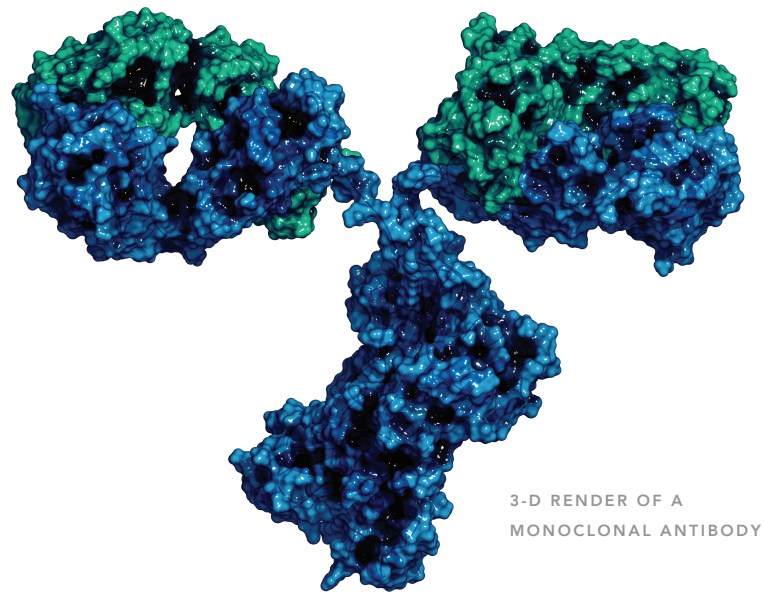
In total, 142 patients received the biosimilar between May 22 and July 26, 2017. Infusion-related AEs were noted from nursing infusion records and graded using Common Terminology Criteria for Adverse Events, version 4.03.

Patients who had been receiving the reference product as a rapid infusion continued at this rate with the biosimilar. Those who had received just 1 prior dose of the reference product at the standard first-dose infusion rate got their first dose of the biosimilar as a rapid infusion.

Patients who had not received the reference product for over 6 months or were rituximab-naïve received their first dose at the standard first-dose infusion rate. If that was well tolerated, subsequent doses were given as rapid infusion. All patients received premedication with acetaminophen and an antihistamine.

The study results showed that the rapid infusion of the biosimilar was well tolerated in all 3 groups. In addition, patients who switched from the reference safely received their first dose of the biosimilar as a rapid infusion. One patient who switched from the reference developed tachycardia during the first dose of the biosimilar at a rapid infusion rate; however, this patient was able to receive subsequent doses of the biosimilar with an added glucocorticoid premedication without further IRRs.

Grade 2 or 3 IRRs were observed with 8 first-rate infusions (12%), and 4 patients received further doses of the biosimilar. They received their next doses at the standard subsequent infusion rate with glucocorticoid premedication without incident, and 2 of the patients received further doses at a rapid infusion rate without an IRR.

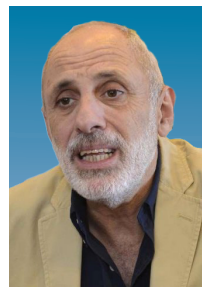


3-D RENDER OF A MONOCLONAL ANTIBODY

These results—the first reported postmarketing experience of rapid infusion of biosimilar rituximab—showed that patients can be safely switched from the reference product to rituximab biosimilar without reverting to slower infusion rates. The authors said they hope that these findings will facilitate the introduction of the biosimilar at centers prescribing rituximab without adversely affecting use of resources or the patient experience.

Argentine-Approved Novex Has Similar Safety Profile to MabThera

Gustavo Milone, MD, and his team presented a study that investigates the postmarketing trends of Novex, a biosimilar rituximab approved in Argentina for the same indications as the reference product (MabThera, Rituxan).[2] Postmarketing surveillance data from the first national pharmacovigilance plan for a biosimilar monoclonal antibody show that, in terms of tolerability, this biosimilar has a similar safety profile to that of the reference product.



MILONE

To determine deviations from expected frequencies of adverse events (AEs), a prospective treatment registry was implemented from the start of the biosimilar's commercialization on November 26, 2014, with data reported until June 30, 2017. Physicians—180 in total—tracked age, gender, indication, dose, dose frequency, and date of treatment initiation and finalization for each patient receiving the biosimilar.

The study comprised the records of 525 patients who had at least 1 follow-up. Most were female (52%), the mean age was 63.3 years (range, 10-90), and most received the biosimilar rituximab for hematological disease (91.2% of cases). The treatment duration ranged from 154 to 309 days, with the number of treatment cycles varying from 1 to 12. Individual Case Safety Reports were collected from 24 patients with 29 AEs. The most frequently reported were acute infusion-related reaction (14), arrhythmia (3), pneumonia (2), and stroke (2).

The researchers noted that 41 treatments with rituximab were initiated before the product launched and, assuming treatment began with MabThera, imply switching to the biosimilar from the reference.

Researchers investigating data from the postmarketing surveillance found a similar incidence of AEs after the use of rituximab biosimilar compared with the published data of the reference product. Thus, in terms of tolerability, the biosimilar and its reference have similar safety profiles. ◆

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At the American Society of Hematology's 59th Annual Meeting and Exposition, healthcare industry leaders sat down with *The American Journal of Managed Care®* to speak about what's new and important about changes in healthcare. Access the video clips at ajmc.com/conferences/ash-2017.

Dr Stephen Schuster Outlines CAR T Results Seen in Leukemia, Lymphoma, and Myeloma

Stephen Schuster, MD, of the Perelman School of Medicine at the University of Pennsylvania provides a summary of results seen with chimeric antigen receptor (CAR) T-cell treatments in leukemia, lymphoma, and myeloma.

What have been the promising results seen in CAR T-cell treatments for patients with leukemia, lymphoma, and myeloma?

There are lots of promising results in leukemia and lymphoma. The myeloma results are early, but the leukemia and lymphoma results have already translated into 2 commercially available products. The leukemia, specifically, is B-cell acute lymphoblastic leukemia [ALL], [which is] the leukemia that is most common in children. The target of therapy is CD19, so this is CARs directed against CD19, which is on the surface of B-cell ALL. And there, there's an 80% response rate, and at 1 year, 75% of the kids are in good shape, in remission. And these are kids with ALL, who have disease that is either recurred after standard therapy or doesn't respond to standard therapy or [who] have had transplants and have recurrence after transplants. So, it offers a potentially long-term, durable remission for these kids.

The lymphoma indication, so far, is diffuse large B-cell lymphoma, and there we have roughly 40% remission rates, regardless of which study you're talking about and which CAR T cell you're talking about—and they're durable. So, I have some of the longest follow-up, which I published [December 10, 2017] in the *New England Journal of Medicine*, and these patients in remission, it lasts for years. The median follow-up in that report was 29 months, and none of the respondents had relapsed. So, this is a breakthrough for relapsed/refractory lymphoma patients who don't respond to conventional therapies or to salvage therapies.

With regard to myeloma, they're at about where lymphoma was 3 years ago. They need more trials with larger numbers of patients and longer follow-up, but preliminarily, the target, [B-cell maturation antigen] on the malignant plasma cells of myeloma, looks very susceptible to the CAR T approach. Lots of things about CAR T at this meeting; it's clear to me that CAR T cells are a paradigm and we can make CAR T cells to any specific tumor antigens or viral antigens, for that matter, and have a T-cell therapeutic approach. ◆

Dr Julie Wolfson Highlights Different Outcomes in AYAs With ALL Compared With Children

Adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL) tend to have worse outcomes than children with ALL. New research published at the 59th American Society of Hematology Annual Meeting and Exposition delved into the reasons why, explained Julie A. Wolfson, MD, of the University of Alabama at Birmingham School of Medicine.

How do outcomes of AYAs with ALL differ from children?

Adolescents and young adults, or AYAs, the National Cancer Institute defines as patients who are diagnosed with cancer between the ages of 15 and 39. AYAs with ALL, in specific, have poor survival compared with children. So, children, in our study, we had comparable survival to what's been shown nationally before, which is about 70% to 80% depending on their age; in AYAs, it's more 35% to 45%, depending on the age, as well.

What are the reasons for the differences in outcomes between AYAs and children?

So that's a really important question, and it's something that we're really all trying to get to the bottom of. In our study, what we looked at was, in specific, in AYAs what predicted that poor survival. And there were 2 different times when they relapsed, and in terms of the risk of that relapse, we found that if they were going to relapse on therapy, there was about a 2.2-fold increased risk in patients on therapy if they were from nonwhite races or ethnicities. And there was a 2.6-fold increased risk of relapse if they were not enrolled on a clinical trial compared with patients that were enrolled on a clinical trial.

But then when we looked at the risk of relapse after they finished treatment, it was actually the duration of therapy. So, for each additional month of maintenance treatment that they had, there was a 30% decreased risk of relapse, and for each additional month of consolidation treatment, there was a 20% decreased risk of relapse. There was also a trend toward association with socioeconomic status and insurance there. ◆

Dr Joshua Richter Discusses the Patient Financial Burden of New Treatments and Cures

This is a critical time for the healthcare industry to evaluate how patients are financially burdened by novel treatments that promise tremendous outcomes, said Joshua R. Richter, MD, of the John Theurer Cancer Center.

As new, more expensive treatments improve survival, how can clinicians identify and address the burden of financial toxicity?

I think this is something that's really critical and is becoming more and more of an issue: that we can no longer, as physicians, bury our heads in the sand. [We] need to understand where the difficulty comes in with this. We have a lot of new drugs, and these drugs may offer many of our patients tremendous outcomes. But there is also a significant amount of financial burden that does come across, not only to the patient, but to their family. And while some of this is simply perceived by the patient, some of this can be quite real and patients often plunge themselves into deep financial trouble in order to support the care for their own disease, and this may affect the family, as well.

So, this is really kind of a critical time for us to evaluate things on a global standpoint. Yes, we need to be concerned about the system as a whole, but we need to get more granular and focus on what are the deleterious effects that we're seeing on a patient-by-patient level in terms of the financial burden that we're seeing with these great new therapies. ◆

Dr Thomas LeBlanc: Patients With Blood Cancers Less Likely to Use Hospice Care

Patients with blood cancers tend to use hospice care services less frequently overall than patients with solid tumors. Although there has been an increase in hospice care use among patients with blood cancers, there has been a failure to increase hospice use meaningfully, according to Thomas LeBlanc, MD, of the Duke Cancer Institute.

How does hospice use differ between patients with blood cancer and patients with solid tumors?

We know from multiple papers and the literature that patients with blood cancers tend to use hospice care services less frequently overall than patients with solid organ tumors. This is something that's been shown repeatedly over time and something that we don't entirely understand, but we do have some ideas about in terms of what might be driving this difference. The research that we presented at this year's ASH Annual Meeting included some evidence that hospice use probably is increasing, actually, in hematology. We looked specifically at Medicare beneficiaries in the SEER [Surveillance, Epidemiology and End Results] data set who have leukemias of various types, so both acute leukemia and chronic leukemia. We saw a significant increase in hospice use between 2001 and 2011, from about 35% in 2001 up to almost 50% in 2011.

Another study presented at this year's ASH Annual Meeting showed a similar increase in patients with multiple myeloma. However, what we're also seeing is a failure to increase hospice use meaningfully, and what I mean by that is, patients with hematologic malignancies, when they do use hospice, which again is less frequently than those with solid tumors, tend to use it for a lot shorter period of time. We found an average hospice length of stay of only about 9 days among hematological malignancy patients with leukemias.

More concerning, though, we found that those who are dependent on transfusions before hospice referral only used hospice for about 6 days. Those who do hospice care will tell you that using hospice care for just a few hours or a few days, or even maybe a week or two, is really not enough to derive the maximal benefits for patients and families when we know that it is really high-quality care for those who are at the end of life who need that care, in terms of improving how they feel and their ability to stay at home when their time is short. ◆

Dr Nina Shah on the Benefits of Outpatient HSCT When Possible

Providing outpatient hematopoietic stem cell transplant (HSCT) when patients are eligible is a good way to reduce costs without impacting outcomes, explained Nina Shah, MD, associate professor, University of California, San Francisco School of Medicine.

Would it be more cost-efficient to conduct outpatient HSCT if outcomes are comparable and proven safe compared with inpatient transplant?

We just published a paper on this, this year from a large group of patients. And what we know is, for patients who are eligible—and this is often a decision that's between the physician and the patient—patients who are eligible for an outpatient transplant, they do great. They do just as well. And there is less cost to the entire medical system.

I think that if we're going to use that approach, we have to get insurance companies to get on board to help patients pay for things like, for example, hotel rooms near the transplant center or helping a caregiver with their off time from work. And that will actually be more cost-efficient than having the patient in the hospital for 16, 18, 20 days. And patients actually feel more free, that they can do things a little more freely without being tied to a hospital bed. So, I'd really like to see us work together with the payers. ◆

Dr Derek Raghavan Outlines Challenges to Implementing Evidence-Based Guidelines

Physician belief in the art of medicine is running up against the challenge of costs being shifted to patients and health systems and the desire of payers to have less variation in care, said Derek Raghavan, MD, PhD, FACP, FRACP, president, Carolinas HealthCare System's Levine Cancer Institute.

What are the culture challenges that make it difficult for health systems and practices to implement evidence-based guidelines?

It's becoming increasingly challenging to structure our approach to medicine, and there are a whole bunch of issues that get in the way. I think the first, and most important one, is the territorial imperative of the physician. Most physicians like to be independent. They believe in the art of medicine. They feel there is a nuance that will be available with their own personal skill. And, to be truthful, there is something to be said for that. The art of medicine is important. The more experienced physician is going to be, probably, better than the less experienced physician. Part of the difficulty is that some of the art of medicine is predicated on opinion rather than fact.

The second issue that is very challenging at the moment is the fact that we can no longer provide the medical care that we have traditionally with the money that's available to support it. Costs are being shifted to patients; costs are being shifted to healthcare systems. So, there's a tension that is driven by that. The people who pay for healthcare, whether it's governments or health insurance funds, are looking for less variation and more structure and a bigger evidence base.

There has been a symposium at the American Society of Hematology meeting focused on the use of guidelines and how to disperse those guidelines into clinical practice, thinking about the impediments to the use of guidelines by physicians. ◆

Dr Kerry Rogers: Ibrutinib's Impact on Vaccine Response

Ibrutinib has the potential to improve vaccine response for patients with chronic lymphocytic leukemia, and an ongoing trial will help provide a better understanding, explained Kerry Rogers, MD, assistant professor, internal medicine, Division of Hematology, The Ohio State University Comprehensive Cancer Center.

How does vaccination influence the response of patients with chronic lymphocytic leukemia to ibrutinib?

Ibrutinib is an immune-modulatory agent, so it has the potential to improve vaccine responses. However, we don't have enough data [that are] looking at this yet to have a firm conclusion as to how ibrutinib affects this. We have an ongoing study that looks at vaccinating people and then treating them with ibrutinib or treating them with ibrutinib and treating them with vaccines that will answer the question as to whether or not ibrutinib can boost vaccine responses. We suspect, based on its immunologic actions, that it might, but that is something that we'll have to see. ◆

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