Cardio-Oncology Specialists Seek to Optimize Long-term Treatment Outcomes

PEER EXCHANGE
Experts Examine How Targeted Agents Are Reshaping the SOLID TUMOR Landscape

OncPathways
CEACAM5 Joins a Growing Menu of Emerging LUNG CANCER Targets

EHA CONFERENCE HIGHLIGHTS
Novel Combinations for HEMATOLOGIC MALIGNANCIES Are Among the Highlights

RAPID READOUTS
Global Real-World Data Establishes Y-90 Glass Microspheres as Optimal Choice for HCC

CLINICAL TRIAL IN FOCUS
ULTRA-V Trial Seeks to Boost Efficacy With Novel Triplet in CLL

CLINICAL PERSPECTIVES
Suresh S. Ramalingam, MD, FACP, discusses EGFR Exon 20 Insertion+ Advanced NSCLC

UAMS WINTHROP P. ROCKEFELLER CANCER INSTITUTE
Comprehensive Treatment Advances Care for Patients With Early-Stage Breast Cancer

by Gwendolyn M. Bryant-Smith, MD, Christopher Jean-Louis, DO, MPH; and Ronda S. Henry-Tillman, MD
For **HIGHER-RISK MDS**

**ISN’T IT TIME TO TRANSFORM SURVIVAL OUTCOMES?**

Newly diagnosed patients with higher-risk myelodysplastic syndromes (HR-MDS) face poor outcomes

1. **12.4 months mOS in a real-world study**

2. ~40% of patients transform to AML

One class of agents is not enough—**new options that can be used in combination** with HMAs are urgently needed

---

*Observed in a real-world evaluation of a total 1101 adult patients, 825 with HR-MDS (defined by an IPSS score of intermediate-2 or high risk) and 276 with low-blast count AML (defined by 21-30% blasts) treated with azacitidine between 2010 and 2016 in Ontario, Canada. Transfusion dependence was determined by the Nordic Score definition of transfusion dependence: ≥2 units of blood transfused per 4 weeks.*

Based on a 2018 review of transformation to secondary AML in MDS patients, as well as a 2016 multicenter, retrospective study of 7319 untreated MDS patients from 19 institutional databases. Risk of transforming to AML from HR-MDS was determined by IPSS and IPSS-R.†

AML=acute myeloid leukemia; HMAs=hypomethylating agents; HR-MDS=higher-risk myelodysplastic syndromes; IPSS=International Prognostic Scoring System; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndromes; mOS=median overall survival.

References:

*All trademarks are the property of their respective owners. ©2021 Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. All rights reserved. 04/21 US-NON-0155*
EDITOR IN CHIEF

MAURIE MARKMAN, MD
President
Medicine & Science
Cancer Treatment Centers of America
Philadelphia, PA

Ghassan K. Abou-Alfa, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Kenneth C. Anderson, MD
Dana-Farber Cancer Institute
Boston, MA

Arjun V. Balar, MD
NYU Langone Medical Center
New York, NY

Tanios Bekaii-Saab, MD, FACP
Mayo Clinic Cancer Center
Phoenix, AZ

Johanna C. Bendell, MD
Sarah Cannon Research Institute/Tennessee Oncology
Nashville, TN

Michael J. Birrer, MD, PhD
University of Arkansas for Medical Sciences
Winthrop P. Rockefeller Cancer Institute
Little Rock, AR

Patrick I. Borgen, MD
Maimonides Medical Center
Brooklyn, NY

Jennifer R. Brown, MD, PhD
Dana-Farber Cancer Institute
Boston, MA

Adam M. Brufsky, MD, PhD
University of Pittsburgh Medical Center
Pittsburgh, PA

Howard “Skip” Burris III, MD
Sarah Cannon Research Institute/Tennessee Oncology
Nashville, TN

Barbara A. Burtness, MD
Yale Cancer Center
New Haven, CT

Ezra Cohen, MD
Moores Cancer Center
UC San Diego Health
La Jolla, CA

Jorge E. Cortes, MD
Augusta University
Georgia Cancer Center
Augusta, GA

Jeffrey Crawford, MD
Duke University School of Medicine
Durham, NC

Roy S. Herbst MD, PhD
Smilow Cancer Hospital
Yale New Haven Health
New Haven, CT

Howard S. Hochster, MD
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ

Leora Horn, MD, MSc
Vanderbilt-Ingram Cancer Center
Nashville, TN

Sara A. Hurvitz, MD
David Geffen School of Medicine at UCLA
Santa Monica, CA

Thomas Hutson, DO, PharmD
Texas Oncology/Baylor Charles A. Sammons Cancer Center
Dallas, TX

Joyce A. O’Shaughnessy, MD
Texas Oncology/Baylor Charles A. Sammons Cancer Center
Dallas, TX

Sumanta Kumar Pal, MD
City Of Hope
Duarte, CA

Andrew L. Pecora, MD, CPE
John Thuerer Cancer Center
Hackensack, NJ

Roman Perez-Soler, MD
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, NY

Daniel P. Petrylak, MD
MD Anderson Cancer Center
Houston, TX

Philip Philip, MD, PhD
Barbara Ann Karmanos Cancer Institute
Detroit, MI

Elizabeth R. Plimack, MD, MS
Fox Chase Cancer Center
Philadelphia, PA

Suresh S. Ramalingam, MD
Wincinsip Cancer Institute of Emory University
Atlanta, GA

Adam I. Riker, MD
Louisiana State University, School of Medicine
New Orleans, LA

Brian I. Rini, MD
Vanderbilt-Ingram Cancer Center
Nashville, TN

Hope S. Rugo, MD, FASCO
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA

Nabil F. Saba MD
Wincinsip Cancer Institute of Emory University
Atlanta, GA

A. Oliver Sartor, MD
Tuane University School of Medicine
New Orleans, LA

Lee S. Schwartzberg, MD
West Cancer Center
Germantown, TN

Andrew D. Seidman, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Lecia V. Sequist, MD
Massachusetts General Hospital
Boston, MA

George R. Simon, MD
Moffitt Cancer Center
Tampa, FL

Debu Tripathy, MD
The University of Texas MD Anderson Cancer Center
Houston, TX

Brian Van Tine, MD, PhD
Washington University School of Medicine
Siteman Cancer Center
St. Louis, MO

Alan P. Venook, MD
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA

Nicholas J. Vogelzang, MD
Comprehensive Cancer Centers of Nevada
Las Vegas, NV

Everett E. Vokes, MD
University of Chicago Medicine
Chicago, IL

Heather A. Wakelee, MD
Stanford University Medical Center
Stanford, CA

Jeffrey S. Weber, MD, PhD
NYU Langone Medical Center
New York, NY

Jared Weiss, MD
University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, NC

Howard (Jack) West, MD
City of Hope
Duarte, CA

William G. Wierda, MD, PhD
The University of Texas MD Anderson Cancer Center
Houston, TX

Vol. 22 | No. 15 | AUGUST 2021
blovely@mjhlifesciences.com
Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 60.
OncologyLive®

Vol. 22 / No. 15 / AUGUST 2021
www.OncLive.com

Cardio-oncology Specialists
Pave Optimal Treatment Path for Patients With Cancer

by MEIR RINDE

Investigative efforts concerning cardiotoxic effects of anticancer therapies have flourished, and the subspecialty of cardio-oncology has grown rapidly in recent years. As cancer survival rates continue to improve, a great deal remains unknown about the long-term cardiovascular treatment effects associated with cancer therapies.

From the Editor
Challenges Arise as Public Health and Scientific Communication Enters Uncharted Territory
By Maurie Markman, MD

Medical World News®

FDA Digest
19 Drug Spotlight:
Infritaginitib (Truseltiq)
20 Sotorasib (Lumakras)

ONCOLOGY & BIOTECH NEWS®

EUROPEAN HEMATOLOGY ASSOCIATION
2021 VIRTUAL ANNUAL CONGRESS
33 Fixed-Duration Venetoclax/Obinutuzumab Improves Outcomes for Patients With CLL
34 Updated Analysis of Prognostic and Predictive Values of Genomic Aberrations in CLL14 Trial
37 Axi-Cel Induces Superior Survival in R/R Follicular Lymphoma vs Historical Controls
38 Naratumab Emantine/Rituximab Combo Elicits Clinical Activity in Relapsed/Refractory DLBCL

Clinical Trial in Focus
40 Investigators Look to Enhance Response With Triplet in CLL

Clinical Perspectives
49 Brigatinib Maintains Long-Term Efficacy in Crizotinib-Refractory ALK+ NSCLC

Subscribe to receive news you can use
Get the latest breaking news, specialty coverage, and conference coverage sent straight to your inbox and/or mailbox.
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes  

SAME POWERFUL EFFICACY. 
FASTER ADMINISTRATION.  

Approved across 5 indications spanning a wide range of multiple myeloma patients

INDICATIONS 
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:

• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant  
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy  
• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy  
• as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION 
CONTRAINDICATIONS 
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS 
Hypersensitivity and Other Administration Reactions 
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions 
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions 
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
~3 to 5 minute administration

- Subcutaneous injection is substantially faster than intravenous daratumumab. The recommended dose of DARZALEX FASPRO™ is 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously over ~3 to 5 minutes. DARZALEX FASPRO™ is for subcutaneous use only. Do not administer intravenously.

See the Dosage and Administration section of the prescribing information for dosing considerations and dosing schedules for approved regimens.

See Important Safety Information below for hypersensitivity and administration reactions, pre-medication and post-medication requirements, and other important considerations for use of DARZALEX FASPRO™.

Efficacy consistent with intravenous daratumumab

- DARZALEX FASPRO™ demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients:
  - ORR was 41% (95% CI: 35%, 47%) for DARZALEX FASPRO™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259).
  - Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent.
  - In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with lenalidomide and dexamethasone (Drd) was evaluated in 65 patients with multiple myeloma who had received ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%).
  - In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%).

Fewer systemic ARRs vs intravenous daratumumab

- Nearly 3x reduction in systemic administration-related reactions (ARRs) with DARZALEX FASPRO™ vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZALEX FASPRO™ had a systemic ARR of any grade vs 34% with intravenous daratumumab).
- Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™. See Important Safety Information for more details.

*For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.

In clinical trials of DARZALEX FASPRO™, DARZALEX® (daratumumab), and the Prescribing Information for DARZALEX®, the term “infusion reactions” was used instead of “systemic administration-related reactions.”

Neutropenia

Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO™, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO™ can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO™ and for 3 months after the last dose.

The combination of DARZALEX FASPRO™ with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO™-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The most common adverse reaction (≥20%) with DARZALEX FASPRO™ monotherapy is: upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematology laboratory abnormalities (≥40%) with DARZALEX FASPRO™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.
injection-site reaction was injection site erythema. These local reactions in this pooled safety population, injection-site reactions occurred in 8% of patients who received DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions, including severe or life-threatening (Grade 4) administration-related reactions, immediately after daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum (see References). The determination of a patient’s ABO and Rh blood type are not impacted (see Drug Interactions).

In a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids (see Dosage and Administration (2.3) in Full Prescribing Information). Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.3) in Full Prescribing Information). Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions have occurred in a median of 7 minutes (range: 9 minutes to 4.7 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 5 months after the last dose (see Use in Specific Populations). The combination of DARZALEX FASPRO with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum (see References). The determination of a patient’s ABO and Rh blood type are not impacted (see Drug Interactions).

In addition to transfusion centers, this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Tyrosine and screen patients prior to starting DARZALEX FASPRO (see Dosage and Administration (2.1) in Full Prescribing Information).

Interference with Determination of Complete Response

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. Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see Drug Interactions). This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
- Neutropenia [see Warning and Precautions].
- Thrombocytopenia [see Warning and Precautions].
- Clinical Trials Experience

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

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES (see Clinical Studies (14.1) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,670 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fetal adverse reactions occurred in 3.0% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 2.6% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

DOSAGE INTERRUPTIONS

Dose interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia. The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>7%</td>
</tr>
</tbody>
</table>

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

| DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) (N=67) |
|------------------|----------------|---------------|
| Infections       |                |               |
| Upper respiratory tract infection | 39 | 0 |
| Bronchitis       | 16 | 0 |
| Pneumonia        | 15 | 7% |
**DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection**

**Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (continued)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>3*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>13</td>
<td>14*</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>34</td>
<td>14*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
<td>3*</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
<td>3*</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1*</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>6*</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>3*</td>
</tr>
<tr>
<td><strong>Respiratory disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
<td>2*</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>2*</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>43</td>
<td>2*</td>
</tr>
<tr>
<td><strong>Lower respiratory tract infection</strong></td>
<td>14</td>
<td>2*</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle pains</td>
<td>31</td>
<td>2*</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5*</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9*</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.

**Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) include:**

- **General disorders and administration site conditions:** infection reaction, injection site reaction, chills
- **Infections:** herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** headache, paresthesia
- **Metabolism and nutrition disorders:** hypocalcemia, hyperglycemia
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, pulmonary edema
- **Cardiac disorders:** atrial fibrillation

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

**Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>96 % / 52 %</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93 % / 84 %</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93 % / 42 %</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88 % / 49 %</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48 % / 19 %</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-VMP (N=67).

**Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5*</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2*</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
<td>2*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
<td>2*</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle pains</td>
<td>31</td>
<td>2*</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5*</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9*</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fatigue includes asthenia, and fatigue.

**DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection**

**In Combination with Lenalidomide and Dexamethasone**

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, inflammation, dyspnea, and blood creatinine increased. The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 3 summarizes the adverse reactions in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.
**DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection**

- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain
- Nervous system disorders: dizziness, headache, paresthesia
- Skin and subcutaneous tissue disorders: rash, pruritus
- Gastrointestinal disorders: abdominal pain
- Infections: esophagitis, herpes zoster
- Metabolism and nutrition disorders: decreased appetite
- Cardiac disorders: atrial fibrillation
- General disorders and administration site conditions: chills, infusion reaction, injection site reaction
- Vascular disorders: hypotension, hypertension

Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

### Table 4: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leucocytes</td>
<td>94</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>96</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with D-Rd (N=65).

**Monotherapy**

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously of daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 28% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5%. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >3% of patients included thrombocytopenia. The most common adverse reaction (≥20%) was upper respiratory tract infection. Table 5 summarizes the adverse reactions in COLUMBA.

### Table 5: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infusion reactions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;h&lt;/sup&gt;</td>
<td>9</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>b</sup> Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.
<sup>c</sup> Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jiroveci pneumonia, and pneumonia.
<sup>d</sup> Fatigue includes asthenia, and fatigue.

### Table 6: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
<th>Intravenous Daratumumab&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leucocytes</td>
<td>65</td>
<td>19</td>
<td>57</td>
<td>76</td>
<td>57</td>
<td>14</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>59</td>
<td>36</td>
<td>56</td>
<td>93</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>43</td>
<td>16</td>
<td>45</td>
<td>43</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>42</td>
<td>14</td>
<td>39</td>
<td>39</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. 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 the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

Treatment-emergent anti-daratumumab antibodies were tested in 451 patients treated with DARZALEX FASPRO as monotherapy or as part of a combination therapy. One patient (0.2%) who received DARZALEX FASPRO as monotherapy tested positive for anti-daratumumab antibodies and transient neutralizing antibodies. However, the incidence of antibody development might not have been reliably determined because the assays that were used have limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab.

Treatment-emergent anti-rHuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (16/192) of patients who received DARZALEX FASPRO as part of combination therapy. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposures. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

**Postmarketing Experience**

The following adverse reactions have been identified with use of intravenous daratumumab (N=260) and Intravenous Daratumumab (N=258).

- Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.
- Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jiroveci pneumonia, and pneumonia.
- Fatigue includes asthenia, and fatigue.
- Infusion reactions includes terms determined by investigators to be related to infusion.
- Cough includes cough, and productive cough.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Only grade 3 adverse reactions occurred.
- Grade 5 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO include:

- General disorders and administration site conditions: injection site reaction, peripheral edema
- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, muscle spasms
- Gastrointestinal disorders: constipation, vomiting, abdominal pain, nausea
- Metabolism and nutrition disorders: decreased appetite, hyperglycemia, hypocalcemia, dehdyration
- Psychiatric disorders: insomnia
- Vascular disorders: hypertension, hypotension
- Nervous system disorders: dizziness, peripheral sensory neuropathy, paresthesia
- Infections: bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B reactivation
- Skin and subcutaneous tissue disorders: pruritus, rash
- Cardiac disorders: atrial fibrillation
- Respiratory, thoracic and mediastinal disorders: pulmonary edema

**Immune System:**

- Anaphylactic reaction
- Gastrointestinal: Pancreatitis
**Labour and Delivery**

There were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

**Women and Males of Reproductive Potential**

**Embryo-Fetal Toxicity**

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

**Hypersensitivity and Other Administration Reactions**

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see Warnings and Precautions].

**Thrombocytopenia**

Advise patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

**Contraception**

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for at least 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

**Pediatric Use**

There is no data on the presence of daratumumab and hyaluronidase-filh in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant milk suspensions in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide prescribing information for additional information.

**Data**

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

**REFERENCES**

Long-term Outcomes Rely on Innovative Care Paths

SURVIVAL OUTCOMES FOR PATIENTS with cancer are improving rapidly across a variety of malignancies. As long-term follow-up data begins to arrive for novel treatment strategies, questions surrounding the lasting adverse effects of these therapies are starting to come into focus.

Documented adverse effects from radiation and chemotherapy have shown that patients with cancer develop cardiac conditions including damage to valves of the heart, hypertension, or heart failure. For example, trastuzumab (Herceptin), the HER2-directed monoclonal antibody, has been scrutinized as it is associated with high rates of cardiac function declines. Results from 1 retrospective study of 408 patients, found a decline in abnormal left ventricular ejection fraction in 43.9% of patients with breast cancer who had normal levels prior to treatment.¹

Cardio-oncology, a specialized field of exploration, is attempting to contextualize and mitigate the severity of cardiotoxicities associated with the latest therapies. Additionally, despite the availability of cardioprotective therapies, their effectiveness in conjunction with anticancer therapies remain unknown. Our cover story explores the state of the treatment landscape in relation to cardiotoxic effects, as several investigators in the cardio-oncology specialty provide insights on the rapidly evolving complications that arise in tandem with new therapies.

“As much as we have made progress with cardio-oncology, we are still really in a very early phase of the specialty, and there are probably still more questions than answers,” said Michael G. Fradley, MD, an associate professor of clinical medicine and medical director of the Thalheimer Center for Cardio-Oncology at Penn Medicine in Philadelphia, Pennsylvania.

Cardiotoxic effects are only 1 point of interest in terms of survivorship considerations. Neuropathy, fertility, bone health, fatigue, and alopecia are all chronic and pressing effects of long-term treatment for patients. Programs such as the 19th Annual School of Breast Oncology, sponsored by Physicians’ Education Resource®, LLC (PER®) now include panels on uncontrolled treatment-related symptoms for patients with cancer. Meeting chair, Joyce A. O’Shaughnessy, MD, will lead the 3-day hybrid event scheduled for October 28 to 30, and put into context mitigation strategies for breast oncologists and discuss the latest investigative efforts aimed at the prevention and treatment of these effects.

For more information and to register for this and other events, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCE
Challenges Arise as Public Health and Scientific Communication Enters Uncharted Territory

by MAURIE MARKMAN, MD

IT IS DIFFICULT TO DISPUTE that these are troubling times for government officials and public health agencies. Consider the residents of California, who have been facing unprecedented heat and drought. In many regions of the state, officials have asked the public to carefully conserve water and electricity and the potential for wildfires in the coming months is of great concern. In addition to environmental factors, in September a rare gubernatorial election will take place in the state in response to the sitting governor’s actions and decisions during the COVID-19 pandemic.

Further, the rapid spread of the COVID-19 delta variant, currently the most common variant in the United States, has become a concern both at home and abroad. How should governments and public health agencies respond? Many officials and individuals appear to believe the pandemic is coming to an end, but objective data challenge this view. For example, in the United Kingdom the delta variant is responsible for at least 90% of all infections and there is worrying evidence that the available COVID-19 vaccines, although effective against the variant, are far less beneficial after the first dose of the required 2-dose regimen. According to current estimates, the delta variant is twice as infectious as the alpha variant, the UK’s previously predominant variant.

The situation in the developing world is far worse. A recent report of cases in Africa noted the incidence of 30,000 new cases reported each day, with less than 1% of the population vaccinated. Additionally, the World Health Organization reported that 18 African nations had already used at least 80% of their existing vaccine supplies, with 8 countries reporting that they had no available vaccines.

PUBLIC UNCERTAINTY RESULTS IN CONFLICTING RECOMMENDATIONS

Discussions and controversies associated with how the United States (and other countries) can optimally manage future developments associated with the pandemic are continually evolving. Points of contention include efforts addressing the issue of trust associated with COVID-19 vaccination. For example, reviewing a survey of more than 6000 individuals conducted in October 2020 and March 2021, at which time there was evidence of the approved acceptance of vaccination through regulatory approvals and mass vaccination programs, investigators concluded that “vaccine hesitancy remained high, especially among young adults and Black and low socioeconomic-status participants.”

Continued controversy is also associated with the use of masks and social distancing in general societal interactions, the workplace, and schools. The apparent disagreement between the CDC in the United States and declarations emanating from the World Health Organization has likely added a disturbing element of confusion for local and state public health officials who are attempting to make rational recommendations to government leaders.

The list of COVID-19–related scientific concerns does not end here, especially as we learn more about the nature and severity of persistent symptoms lasting longer than 60 days after diagnosis. In addition, much remains to be understood regarding the diagnosis and treatment of multisystem inflammatory syndrome in children who receive a COVID-19 diagnosis. Just how common is this event and is the apparently rare occurrence a relevant justification for active efforts to vaccinate children?

Finally, although few objectively validated adverse events have been reported, some have been serious and even fatal. How should these evolving data influence recommendations for vaccination strategies given how uncommon these events are in the reported real-world experience? Further, how will officials balance multiple pragmatic considerations, including the availability of specific vaccines within a given health care authority?

MITIGATING TRUST ISSUES IN SCIENTIFIC COMMUNICATION

The goal of this commentary is not to resolve these issues but to emphasize the magnitude of the potential concerns to be confronted. Unfortunately, in addition to the issues cited above, one must also consider several increasingly disconcerting events that have been widely reported in...
From the Editor

the media. These topics call into question the public’s ability to objectively trust information from various sources and transcend questions related to vaccine products.

Although space does not permit a thorough discussion of these events, some examples include: questions surrounding the complete unwillingness of China to participate in the critical review process of vaccines; concerns regarding potential conflicts of interest among members of the international scientific community involved in research in this arena; an objective lack of valid information related to the clinical utility of Chinese COVID-19 vaccines against evolving variants, and the quite public debate between the manufacturer of one of the mRNA vaccines and the FDA/CDC regarding the need for booster shots. There are also the rapidly evolving events and serious implications related to the FDA's review of potentially inappropriate interactions with a pharmaceutical company in their development of a highly controversial new Alzheimer drug.

This commentary highlights the possibility that such issues could also negatively affect trust in science and public health communication associated with essential efforts in the cancer arena. In this regard, consider the recent report which found that 24% of individuals who refused to receive, or whose parents refused to consent for, the HPV vaccination in 2019 stated that concerns with "safety and adverse events" were the reason for their decision, despite well-established data that unequivocally refute such fears.

REFERENCES

13. @DrWoodcockFDA. Twitter post. Given the ongoing interest and questions, today I have requested that @OIGatHHS conduct an independent review and assessment of interactions between representatives of Biogen and FDA during the process that led to the approval of Aduhelm. Posted July 9, 2021. Accessed July 15, 2021. bit.ly/3eyniu3
**INDICATIONS & USAGE**

MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

**For NTE adult patients with DLBCL who have received at least 1 prior therapy**

**REACH TO SECURE A RESPONSE**

NTE=non-transplant–eligible; DLBCL=diffuse large B-cell lymphoma.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**

None.

**Warnings and Precautions**

**Infusion-Related Reactions**

MONJUVI can cause infusion-related reactions (IRRs). In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication. Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.
INDICATIONS & USAGE

MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

In L-MIND, Grade 3 neutropenia occurred in 25% of patients, including neutropenia, thrombocytopenia, and anemia. In DLBCL, Grade 3 neutropenia occurred in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor complete blood counts (CBC) prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony-stimulating factor (G-CSF) administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.
**SECURE RESPONSE IN SECOND LINE**

*MONJUVI is the first and only FDA-approved treatment for adult patients with DLBCL who have received at least 1 prior therapy, in combination with lenalidomide*

- High ORR reached, with a majority of responders achieving CR
- Response sustained beyond 18 months

**L-MIND study design**

- L-MIND was an open-label, multicenter, single-arm study that evaluated the efficacy and safety of MONJUVI in combination with lenalidomide followed by MONJUVI monotherapy in adult patients with R/R DLBCL after 1 to 3 prior systemic DLBCL therapies, including CD20-containing therapy. The median number of prior therapies was 2.
- Enrolled patients at the time of the trial were not eligible for or refused ASCT.
- Efficacy was established in 71 patients with DLBCL (confirmed by central laboratory) based on best ORR (defined as the proportion of complete and partial responders) and DoR, as assessed by an Independent Review Committee using the International Working Group Response Criteria (Cheson 2007).
- Patients received MONJUVI 12 mg/kg intravenously in combination with lenalidomide (25 mg orally on days 1 to 21 of each 28-day cycle) for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity.

---

NCCN=National Comprehensive Cancer Network; ORR=overall response rate; CR=complete response rate; R/R=relapsed/refractory; PR=partial response rate; CI=confidence interval; DoR=duration of response; ASCT=autologous stem cell transplant.

---

- **Best overall response rate in patients with R/R DLBCL (N=71)**
  - **37% CR**
  - **55% ORR** (n=39; 95% CI: 43%, 67%)
  - **18% PR**

- **Duration of response in patients with R/R DLBCL (n=71)**
  - **Median DoR: 21.7 months**
  - (range: 0, 24)
  - *Kaplan-Meier estimates.*
MONJUVI is the first and only FDA-approved treatment for adult patients with DLBCL who have received at least 1 prior therapy, in combination with lenalidomide.

INDICATIONS & USAGE
MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT). This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION
Warnings and Precautions (cont’d)
Embryo-Fetal Toxicity
Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Adverse Reactions
Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥6% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions (≥20%) were neutropenia (51%), fatigue (38%), anemia (36%), diarrhea (36%), thrombocytopenia (31%), cough (26%), pyrexia (24%), peripheral edema (24%), respiratory tract infection (24%), and decreased appetite (22%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to MORPHOSYS US INC. at (844) 667-1992.

To learn more, visit MonjuviHCP.com
For information about patient assistance, visit MyMissionSupport.com

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

REFERENCES: 1. MONJUVI Prescribing Information. Boston, MA: MorphoSys. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V4.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 24, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
INDICATIONS AND USAGE

MONJUVI, in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

MONJUVI can cause infusion-related reactions. In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication.

Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Myelosuppression

MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12%, and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor CBC prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony-stimulating factor administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections

Fatal and/or serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose. In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Embryo-Fetal Toxicity

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

Clinical Trials Experience

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The safety of MONJUVI was evaluated in L-MIND. Patients (n=81) received MONJUVI 12 mg/kg intravenously in combination with lenalidomide for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Among patients who received MONJUVI, 57% were exposed for 6 months or longer, 42% were exposed for greater than one year, and 24% were exposed for greater than two years.

Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in 36% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebralvascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions (≥ 20%) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

Table 3 summarizes the adverse reactions in L-MIND.

### Table 3: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>38</td>
<td>3.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>1.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>1.2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection†</td>
<td>24</td>
<td>4.9</td>
</tr>
<tr>
<td>Urinary tract infection†</td>
<td>17</td>
<td>4.9</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>1.2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>19</td>
<td>2.5</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fatigue includes asthenia and fatigue
†Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection

Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:

- Blood and lymphatic system disorders: lymphopenia (6%)
- General disorders and administration site conditions: infusion-related reaction (6%)
- Infections: sepsis (4.9%)
- Investigations: weight decreased (4.9%)
- Musculoskeletal and connective tissue disorders: arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- Neoplasms benign, malignant and unspecified: basal cell carcinoma (1.2%)
- Nervous system disorders: headache (5%), paresthesia (7%), dysgeusia (6%)
- Respiratory, thoracic and mediastinal disorders: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- Skin and subcutaneous tissue disorders: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)

MONJUVI® (tafasitamab-cxix)

Initial U.S. Approval: 2020
MONJUVI® (tafasitamab-cxix)

Table 4 summarizes the laboratory abnormalities in L-MIND.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>MONJUVI(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>34</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>20</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>46</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate was 74 based on the number of patients with a baseline value and at least one post-treatment value.

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assays. 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 the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other tafasitamab products may be misleading.

Overall, no treatment-emergent or treatment-booster anti-tafasitamab antibodies were observed. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety profile of tafasitamab-cxix were observed in 2.5% of 81 patients with relapsed or refractory DLBCL with pre-existing anti-tafasitamab antibodies in L-MIND.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. There are no available data on MONJUVI use in pregnant women to evaluate for a drug-associated risk. Animal reproductive toxicity studies have not been conducted with tafasitamab-cxix.

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

MONJUVI is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide prescribing information for additional information. Lenalidomide is only available through a REMS program.

**Clinical Considerations**

Fetal/Neonatal Adverse Reactions

Immunoglobulin G (IgG) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, MONJUVI may cause depletion of fetal CD19 positive immune cells. Defer administering live vaccines to neonates and infants exposed to tafasitamab-cxix in utero until a hematology evaluation is completed.

**Data**

Animal Data

Animal reproductive studies have not been conducted with tafasitamab-cxix. Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

**Lactation**

**Risk Summary**

There are no data on the presence of tafasitamab-cxix in human milk or the effects on the breastfed child or milk production. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to MONJUVI are unknown. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose. Refer to lenalidomide prescribing information for additional information.

**Females and Males of Reproductive Potential**

MONJUVI can cause fetal B-cell depletion when administered to a pregnant woman.

**Pregnancy Testing**

Refer to the prescribing information for lenalidomide for pregnancy testing requirements prior to initiating the combination of MONJUVI with lenalidomide.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose. Additionally, refer to the lenalidomide prescribing information for additional recommendations for contraception.

**Males**

Refer to the lenalidomide prescribing information for recommendations.

**Pediatric Use**

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

**Geriatric Use**

Among 81 patients who received MONJUVI and lenalidomide in L-MIND, 72% were 65 years and older while 38% were 75 years and older. Clinical studies of MONJUVI did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs compared to that of younger subjects. Patients 65 years and older had more serious adverse reactions (57%) than younger patients (39%).

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full prescribing information.
Subcutaneous Daratumumab Plus Pd Gets Go-ahead in Multiple Myeloma

The FDA has approved the combination of daratumumab and hyalurondase-fihj (Darzalex Faspro) plus pomalidomide and dexamethasone (Pd) for the treatment of adult patients with multiple myeloma after receiving at least 1 prior line of therapy including lenalidomide (Revlimid) and a proteasome inhibitor. The decision was supported by data from the phase 3 APOLLO trial (NCT03180736). In data from 304 evaluable patients, daratumumab, a CD38-directed cytolytic antibody, plus hyaluronidase, an endoglycosidase, proved to significantly reduce the risk of progression or death by 37% compared with Pd (HR, 0.63; 95% CI, 0.47-0.85; P = .0018). The median progression-free survival in the investigative arm was 12.4 months (95% CI, 8.3-19.3) vs 6.9 months (95% CI, 5.5-9.3) in the control arm.

The overall response rate was also significantly higher when Pd was added to the subcutaneous formulation. Specifically, the response rate was 68.9% with the combination compared with 46.4% for Pd alone. The stringent complete response rates were 9.3% vs 1.3%, respectively, complete response rates were 15.2% vs 2.6%, very good partial response rates were 26.5% vs 15.7%, and partial response rates were 17.9% vs 26.8%. The minimal residual disease negativity rate was 8.6% (95% CI, 4.7%-14.3%) for the combination compared with 2.0% (95% CI, 0.4%-5.6%) with Pd alone.

Enfortumab Vedotin Gets Green Light and Label Expansion

The FDA has granted a regular approval to enfortumab vedotin-ejfv (Padcev) for patients who have received a prior PD-1/L1 inhibitor and a platinum-containing chemotherapy, and has expanded its indication to include the treatment of adult patients who are ineligible for cisplatin-containing chemotherapy who have received at least 1 prior therapy. The conversion from an accelerated approval to a regular approval and a label expansion for the antibody-drug conjugate (ADC) was based on 2 supplemental biologics license applications that included findings from the phase 3 EV-301 trial (NCT03474107).

Results showed that the median overall survival was 12.9 months (95% CI, 10.6-15.2) for patients who received the ADC (n = 301) vs 9.0 months (95% CI, 8.1-10.7) for patients who received chemotherapy (n = 307; HR, 0.70; 95% CI, 0.56-0.89; P = .001). Further, the median progression-free survival was 5.6 months (95% CI, 5.3-5.8) in the investigative arm vs 3.7 months (95% CI, 3.5-3.9) in the control arm (HR, 0.62; 95% CI, 0.51-0.75; P < .0001). The overall response rate was 40.6% (95% CI, 34.9%-46.5%) with the ADC vs 17.9% (95% CI, 13.7%-22.8%) with chemotherapy.

Companion Diagnostic for Brigatinib Gets Green Light in ALK+ NSCLC

The FDA has approved FoundationOne CDx for use as a companion diagnostic for brigatinib (Alunbrig), which was approved for the frontline treatment of adult patients with ALK-positive metastatic non–small cell lung cancer (NSCLC) in May 2020.

Under this indication, the assay will be used to identify ALK alterations in patients with metastatic NSCLC and determine patients who are potential candidates for brigatinib, a potent and selective next-generation tyrosine kinase inhibitor designed to target ALK molecular alterations.

In May 2020, the FDA approved brigatinib for the first-line or later-line treatment of patients with ALK-positive metastatic NSCLC, based on findings from the open-label phase 3 ALTA-1L trial (NCT02737501), which showed that the agent outperformed crizotinib (Xalkori) with a 51% reduction in the risk of disease progression.

Dose-Escalation Update Is Issued for Neratinib for HER2+ Breast Cancer

The FDA has approved a labeling supplement to the US prescribing information for neratinib (Nerlynx) to include a dose-escalated schedule for patients with HER2-positive breast cancer, which is designed to better support patient needs, including mitigation of diarrhea. The recommended 2-week dose-escalation schedule may be considered for patients instead of starting at the 240 mg daily dose of neratinib. Specifically, the treatment schedule begins with 120 mg daily on days 1 to 7 of week 1; 160 mg daily on days 8 to 14 of week 2; and 240 mg daily beginning week 3 and onwards.

The decision was based on data from the phase 2 CONTROL trial (NCT02400476), which enrolled patients with early-stage, HER2-positive breast cancer who had received loperamide prophylaxis and additional anti-diarrheal treatment as needed, compared with data from patients enrolled in the ExteNET trial (NCT00878709) who had no required dose escalation or anti-diarrheal prophylaxis. Results showed a more than a 60% reduction of patients who experienced grade 3 diarrhea (13% vs 40%). Additionally, a 50% reduction in the median cumulative days of grade 3 diarrhea (5 days vs 2.5 days) and an approximate 80% reduction in discontinuation rates (17% vs 3%) were reported.

NCCN Issues COVID-19 Vaccination Guidance for Patients With Cancer

An expert panel from the National Comprehensive Cancer Network (NCCN) has recommended that patients with cancer receive the COVID-19 vaccine as soon as possible. Large cohort studies have demonstrated that patients with cancer are at high risk of COVID-19 complications and may be sources of prolonged viral shedding and development of variants because they are immunocompromised. The panel noted that this includes those with active cancer who are undergoing treatment, those who are about to be treated, and those who have been treated in the past 6 months.

The guidance indicates that most patients receiving chemotherapy, targeted therapy, immunotherapy, or radiation are safe to be vaccinated. The NCCN also suggests that patients undergoing stem cell transplants, cellular therapy, major surgery, or those with certain forms of acute leukemia receiving initial treatment should delay their vaccinations. Additionally, imaging, such as a PET scan or MRI, should be delayed by 4 to 6 weeks after a patient receives the vaccine if the delay will not cause any harm.

Early data suggest that immunization may not work as strongly in patients with cancer as it does in the general population. The panel has emphasized that patients and close contacts should continue to follow CDC prevaccine recommendations—such as wearing masks, maintaining social distancing, and avoiding crowds—after vaccination to prevent COVID-19.
Drug Spotlight | INFAGRATINIB (TRUSELTIQ)

Infritagrinib Opens Up Options for Patients With FGFR2-Mutant Cholangiocarcinoma

by KYLE DOHERTY

THE IDENTIFICATION OF ACTIONABLE genomic alterations in patients with cholangiocarcinoma has begun to change the standard of care for this patient population. Of particular interest to investigators are FGFR alterations, which have been shown to drive tumorigenesis and are present in approximately 14% of cholangiocarcinoma cases.1

Infritagrinib (Truseltiq), a selective tyrosine kinase inhibitor, has demonstrated activity against tumors with FGFR alterations, eliciting clinically meaningful response rates and tolerable safety profile. The current standard of care for these patients in the second-line setting is chemotherapy, which according to results of a retrospective analysis of 37 patients elicited an overall response rate (ORR) of 5.4% and a median progression-free survival (PFS) of 4.6 months.1

In May, results of the phase 2 CBGJ398X2204 trial (NCT02150947) led to the accelerated approval of infritagrinib for patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test.2

Specifically, the analysis showed that in the 108-patient efficacy population, infritagrinib elicited an ORR of 23% (95% CI, 16%-32%), with 1 patient experiencing a complete response. The median duration of response (DOR) was 5 months (95% CI, 3.7-9.3), and 8 patients (32%) had a DOR of at least 6 months.3

In an interview with OncologyLive®, Milind Javle, MD, a professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, discussed the potential impact of infritagrinib on the treatment landscape of FGFR2 fusion–positive cholangiocarcinoma.

How does this approval shift the cholangiocarcinoma treatment paradigm?

Cholangiocarcinoma is generally treated with first-line chemotherapy, such as gemcitabine and cisplatin, and second-line chemotherapy with FOLFOX. The results [using] both of those approaches are suboptimal. For instance, with FOLFOX, the PFS is [approximately] 4 months, and the overall survival is only 6 months. So now patients with cholangiocarcinoma [harboring] FGFR2 fusions have a viable alternative that is effective in their management, which is for second and subsequent lines of treatment. We hope that in the future, we will be able to use it in earlier lines of therapy.

The patients enrolled in the [CBGJ398X2204] trial had locally advanced or metastatic cholangiocarcinoma or bile duct cancer that had progressed or were intolerant to gemcitabine-based chemotherapy. [Additionally], these were patients with FGFR gene fusions or rearrangements. These patients had been treated previously with chemotherapy. Then, if they had FGFR fusions or rearrangements, they received infritagrinib monotherapy at a dose of 125 mg daily for 21 days.

This study enrolled 120 patients with FGFR2 gene rearrangements or fusions. These patients were then treated with infritagrinib. Several patients were excluded who did not meet the eligibility criteria. In the final analysis, [108 patients were treated] and the ORR, as noted by independent radiological assessment, was 23%. In terms of investigator-assessed response, the response rate was 34%. I also want to mention that the DOR, which was a primary end point of the trial, was 5 months; the DCR was 4% [and the] median PFS was 7.3 months.

What do we know about infritagrinib in terms of safety, and what do clinicians need to be aware of when prescribing it?

The adverse events can be classified into class specific, [which] is specific to all FGFR inhibitors, and then others. The class-specific, FGFR-specific adverse events, which are sort of common to all FGFR inhibitors, include high phosphate level, or hyperphosphatemia, and a proportion [of patients] also [experience] hypophosphatemia. We also have PPE [palmar-planter erythrodysesthesia] syndrome or hand-foot syndrome, mouth sores, and dry mouth. The more significant toxicities, which are mechanism based, include ectopic calcification of the tissues. They also include ocular disorders, such as dry eyes, central serous retinopathy, or retinal pigment epithelial detachment.

What does the future hold for infritagrinib?

[The ongoing trial PROOF trial (NCT03773302) is comparing] infritagrinib to gemcitabine and cisplatin in the first-line setting for patients who have not received prior systemic chemotherapy. The results of that trial should be very informative. We hope that patients can benefit with this targeted therapy and not require any subsequent chemotherapy. However, there are further implications beyond the first-line setting. There are various other combination-therapy trials going on [in which] infritagrinib is being combined with targeted agents and with immunotherapy. I hope that there will be several other alternatives for patients who have FGFR fusions and gene rearrangements.

This [CBGJ398X2204] trial has once again highlighted the importance of molecular sequencing in order to diagnose not just FGFR fusions, but several other targetable or actionable genetic alterations. It is critical that we profile these patients to find these possible avenues.

REFERENCES

In May, results of the phase 2 CBGJ398X2204 trial (NCT02150947) led to the accelerated approval of infritagrinib for patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test.2

Specifically, the analysis showed that in the 108-patient efficacy population, infritagrinib elicited an ORR of 23% (95% CI, 16%-32%), with 1 patient experiencing a complete response. The median duration of response (DOR) was 5 months (95% CI, 3.7-9.3), and 8 patients (32%) had a DOR of at least 6 months.3

In an interview with OncologyLive®, Milind Javle, MD, a professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, discussed the potential impact of infritagrinib on the treatment landscape of FGFR2 fusion–positive cholangiocarcinoma.

How does this approval shift the cholangiocarcinoma treatment paradigm?

Cholangiocarcinoma is generally treated with first-line chemotherapy, such as gemcitabine and cisplatin, and second-line chemotherapy with FOLFOX. The results [using] both of those approaches are suboptimal. For instance, with FOLFOX, the PFS is [approximately] 4 months, and the overall survival is only 6 months. So now patients with cholangiocarcinoma [harboring] FGFR2 fusions have a viable alternative that is effective in their management, which is for second and subsequent lines of treatment. We hope that in the future, we will be able to use it in earlier lines of therapy.

The patients enrolled in the [CBGJ398X2204] trial had locally advanced or metastatic cholangiocarcinoma or bile duct cancer that had progressed or were intolerant to gemcitabine–based chemotherapy. [Additionally], these were patients with FGFR gene fusions or rearrangements. These patients had been treated previously with chemotherapy. Then, if they had FGFR fusions or rearrangements, they received infritagrinib monotherapy at a dose of 125 mg daily for 21 days.

This study enrolled 120 patients with FGFR2 gene rearrangements or fusions. These patients were then treated with infritagrinib. Several patients were excluded who did not meet the eligibility criteria. In the final analysis, [108 patients were treated] and the ORR, as noted by independent radiological assessment, was 23%. In terms of investigator-assessed response, the response rate was 34%. I also want to mention that the DOR, which was a primary end point of the trial, was 5 months; the DCR was 4% [and the] median PFS was 7.3 months.

What do we know about infritagrinib in terms of safety, and what do clinicians need to be aware of when prescribing it?

The adverse events can be classified into class specific, [which] is specific to all FGFR inhibitors, and then others. The class-specific, FGFR-specific adverse events, which are sort of common to all FGFR inhibitors, include high phosphate level, or hyperphosphatemia, and a proportion [of patients] also [experience] hypophosphatemia. We also have PPE [palmar-planter erythrodysesthesia] syndrome or hand-foot syndrome, mouth sores, and dry mouth. The more significant toxicities, which are mechanism based, include ectopic calcification of the tissues. They also include ocular disorders, such as dry eyes, central serous retinopathy, or retinal pigment epithelial detachment.

What does the future hold for infritagrinib?

[The ongoing trial PROOF trial (NCT03773302) is comparing] infritagrinib to gemcitabine and cisplatin in the first-line setting for patients who have not received prior systemic chemotherapy. The results of that trial should be very informative. We hope that patients can benefit with this targeted therapy and not require any subsequent chemotherapy. However, there are further implications beyond the first-line setting. There are various other combination-therapy trials going on [in which] infritagrinib is being combined with targeted agents and with immunotherapy. I hope that there will be several other alternatives for patients who have FGFR fusions and gene rearrangements.

This [CBGJ398X2204] trial has once again highlighted the importance of molecular sequencing in order to diagnose not just FGFR fusions, but several other targetable or actionable genetic alterations. It is critical that we profile these patients to find these possible avenues.

REFERENCES
PIVOTAL CLINICAL TRIAL

CBGJ398X2204 (NCT02150967) was a phase 2, multicenter, open label, single-arm study evaluating the efficacy of infigratinib in patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as determined by local or central testing.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Prior therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (23-81)</td>
<td>46.3% 53.7%</td>
</tr>
</tbody>
</table>

| N = 108 | ≤ 1 | > 1 |

Histological grade

- Well differentiated: 3.8%
- Moderately differentiated: 30.6%
- Poorly differentiated: 40.4%
- Undifferentiated: 15.6%
- Unknown/missing: 0%
- Not applicable: 0%

Metastatic status

- No metastatic site: 4.6%
- Had metastatic site: 95.4%

Site of metastases

- Lung: 68.5%
- Node: 57.4%
- Bone: 25.9%
- Brain: 0%
- Other: 38.0%

CR, complete response; DOR, duration of response; ORR, overall response rate; PR, partial response.

WARNINGS AND PRECAUTIONS

- **Ocular toxicity:** can cause retinal pigment epithelial detachment. Perform a comprehensive ophthalmic examination including optical coherence tomography prior to initiation of infigratinib and at 1 month, 3 months, and every 3 months thereafter during treatment. Withhold as recommended.

- **Hyperphosphatemia and soft tissue mineralization:** Increase in phosphate levels can cause hyperphosphatemia, leading to soft tissue mineralization, cutaneous calcinosis, nonuremic calciphylaxis, vascular calcification, and myocardial calcification. Withhold, dose reduce, or permanently discontinue as recommended.

- **Embryo-fetal toxicity:** can cause fetal harm

EFFECTIVENESS RESULTS IN THE CBGJ398X2204 TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRD population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>23% (16%-32%)</td>
</tr>
<tr>
<td>CR</td>
<td>1%</td>
</tr>
<tr>
<td>PR</td>
<td>22%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>5.0 (3.7-9.3)</td>
</tr>
<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>32%</td>
</tr>
<tr>
<td>Patients with DOR ≥ 12 months</td>
<td>4%</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; ORR, overall response rate; PR, partial response.

COMMONLY REPORTED ADVERSE EFFECTS IN THE CBGJ398X2204 TRIAL

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Infigratinib (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>57%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>56%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>38%</td>
</tr>
<tr>
<td>Constipation</td>
<td>30%</td>
</tr>
<tr>
<td>Palmar-plantar erythrodyssthesia syndrome</td>
<td>33%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>25%</td>
</tr>
</tbody>
</table>

Company: QED Therapeutics Inc

Mechanism of action

- Infigratinib is a small molecule kinase inhibitor of FGFR, with demonstrated activity blocking FGFR signaling and decreasing cell proliferation in cancer cell lines with activating FGFR amplifications, mutations, or fusions. Infigratinib’s half-maximal inhibitory concentrations are 1.1 nM for FGFR1, 1 nM for FGFR2, 2 nM for FGFR3, and 61 nM for FGFR4.

Dose

- 125 mg orally once daily for 21 consecutive days, followed by 7 days off therapy, in 28-day cycles
- Recommended dosage on the same treatment schedule based on comorbidities
  - Mild/moderate renal impairment: 100 mg
  - Mild hepatic impairment: 100 mg
  - Moderate hepatic impairment: 75 mg

Company: QED Therapeutics Inc

REFERENCES


FDA approval—May 28, 2021

The FDA grants accelerated approval for the kinase inhibitor infigratinib (Truseltiq) for the treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test.

Company: QED Therapeutics Inc

FDA approval—May 28, 2021

The FDA grants accelerated approval for the kinase inhibitor infigratinib (Truseltiq) for the treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test.

Company: QED Therapeutics Inc
SOTORASIB (LUMAKRAS), A SMALL MOLECULE inhibitor of KRAS, has been approved as a targeted treatment option for patients with KRAS G12C-mutated locally advanced or metastatic non–small cell lung cancer (NSCLC). KRAS G12C is a driver mutation that is found in about 13% of patients with nonsquamous NSCLC in the United States.

In May, the FDA granted accelerated approval specifically for patients who have progressed on or after at least 1 systemic therapy. The decision was based on data from the phase 2 CodeBreak 100 (NCT03600883) trial, a multicenter, single-arm, open-label clinical study evaluating sotorasib as a therapy for patients whose disease presented with KRAS G12C mutations. In an interview with OncologyLive®, Ferdinandos Skoulidis, MD, PhD, assistant professor of thoracic/head & neck medical oncology at The University of Texas MD Anderson Cancer Center in Houston, discussed the necessity for targeting and screening patients for KRAS G12C mutations. Prescribing physicians need to be aware of 2 specific warnings that are included in the FDA label. The first is the potential for hepatotoxicity, with a requirement for liver function test monitoring every 3 weeks for the first 3 months of treatment and every month thereafter as clinically necessary. The second is the risk of pneumonitis/interstitial lung disease, an infrequent but potentially life-threatening adverse event. It is important to advise patients to immediately withhold sotorasib if they experience new or worsening respiratory symptoms with prompt initiation of diagnostic work up to evaluate for pneumonitis. If drug-related pneumonitis is confirmed, treatment with sotorasib should be permanently discontinued.

How do these data and subsequent approval impact the importance of screening patients for these mutations? The approval of sotorasib underscores the critical importance of offering molecular profiling to every patient with metastatic nonsquamous NSCLC. We now have a well-tolerated approved oral therapy at our disposal that confers durable clinical benefit in about 13% of patients with nonsquamous NSCLC, yet we will only be able to harness its full potential if we can expeditiously identify patients that are candidates for therapy. There is an urgent need to expand and promote equitable access to screening across the US, particularly among underserved patient populations.

With regards to screening for KRAS G12C somatic mutations, both single-gene testing and comprehensive molecular profiling can support treatment with sotorasib. However, broad profiling may offer the additional advantage of simultaneously screening for multiple oncogenic drivers as well as emerging biomarkers.

What does the future hold for sotorasib? We are eagerly awaiting the results of the confirmatory phase 3 randomized CodeBreak 200 clinical trial comparing sotorasib with docetaxel for patients with previously treated advanced KRAS G12C-mutant NSCLC. In this context, an immediate scientific and clinical priority is to comprehensively characterize molecular determinants of response and mechanisms of both innate and acquired resistance to sotorasib to optimally tailor combination regimens. Based on the clinical development paradigm of EGFR tyrosine kinase inhibitors, clinical trials exploring the utility of sotorasib in early-stage, surgically resectable disease are expected to follow.

References

Please discuss the rationale for targeting KRAS G12C mutations and what was noteworthy about the efficacy data.

This specific KRAS G12C mutation is detected in approximately 13% of all patients with metastatic nonsquamous NSCLC. Following failure of standard of care systemic therapies with PD-1/PD-L1 inhibitors and platinum-based chemotherapy administered either in combination or sequentially, clinical outcomes with second-line chemotherapy with docetaxel or docetaxel in combination with ramucirumab for patients bearing KRAS-mutant tumors are generally poor. In addition, chemotherapy is often poorly tolerated and associated with significant toxicities.

Among the most impressive findings of the study were the durability and depth of responses and it should be noted that 4 patients (3.2%) achieved a complete response. The reported overall disease control rate of 80.6% with median progression-free survival of 6.8 months and median overall survival of 12.5 months further support the activity of sotorasib in this heavily pretreated patient population and appear superior to historical data with docetaxel or docetaxel and ramucirumab. The confirmatory phase 3 randomized CodeBreak 200 clinical trial will shed further light on the relative benefit of sotorasib compared to docetaxel.

Finally, it is important to highlight that the clinical activity of sotorasib extended across a broad range of patient subgroups, including difficult-to-treat molecular subsets such as tumors that harbor co-alterations in STK11. This is notable, because STK11 mutations are prevalent in KRAS G12C-mutant NSCLC and are associated with worse clinical outcomes with standard-of-care systemic therapies, including PD-1 axis inhibitor monotherapy, chemoimmunotherapy, platinum-doublet chemotherapy, and chemotherapy with docetaxel.

What adverse effects do clinicians need to be aware of when prescribing sotorasib?

Reported adverse events are generally low-grade and manageable with standard supportive measures, treatment-interruption and, where necessary, up to two dose reductions to 480 mg and 240 mg once a day.
**PIVOTAL CLINICAL TRIAL**

**CodeBreak 100 (NCT03600883)** was a multicenter, single-arm, open-label clinical trial evaluating sotorasib in patients with locally advanced or metastatic KRAS G12C‒mutated NSCLC that has progressed following treatment with an immune checkpoint inhibitor and/or platinum-based chemotherapy. Patients received 960 mg once daily until disease progression or unacceptable toxicity.

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>64 (37-80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 124</td>
<td></td>
</tr>
</tbody>
</table>

**ECOG performance status**

- 30% 0
- 70% 1

**Histology**

- 99% Nonsquamous
- 1% Squamous

**Metastasis at baseline**

- 48% Localized
- 21% Brain
- 21% Bone

**Disease stage at baseline**

- 96% Stage IV
- 4% Stage III

**Number of prior lines of therapy**

- 1: 43%
- 2: 35%
- 3: 23%

**COMMONLY REPORTED ADVERSE EFFECTS IN THE CODEBREAK 100 TRIAL**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Sotorasib (N = 108)</th>
<th>All grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>42%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>35%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>26%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>25%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>16%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>15%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>12%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**EFICACY RESULTS IN THE CODEBREAK 100 TRIAL**

- **ORR (95% CI)**: 36% (28%-45%)
- **CR**: 2%
- **PR**: 35%
- **Median DOR, months (95% CI)**: 10 (1.3+-11.1)
- **Patients with DOR ≥ 6 months**: 58%

**WARNINGS AND PRECAUTIONS**

- **Hepatotoxicity**: Monitor liver function tests every 3 weeks for the first 3 months of treatment and then once monthly as clinically indicated. Withhold, reduce dose, or permanently discontinue sotorasib based on the severity.
- **Interstitial lung disease (ILD)/pneumonitis**: Monitor for new or worsening pulmonary symptoms. Immediately withhold sotorasib for suspected ILD/pneumonitis, and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.

**Mechanism of action**

- Sotorasib is a selective inhibitor of KRAS G12C, forming an irreversible, covalent bond that prevents downstream signaling without affecting signaling of wild-type KRAS.

**How supplied**

- 120-mg tablets

**Dose**

- Swallow tablets whole with or without food
  - 960 mg once daily

**Company**: Amgen

---

**FDA approval—May 28, 2021**

The FDA grants accelerated approval to sotorasib (Lumakras) for the treatment of adult patients with locally advanced or metastatic KRAS G12C–mutant non–small cell lung cancer (NSCLC) who have received at least 1 prior systemic therapy.

**REFERENCES**

THE SUBSPECIALTY OF CARDIO-ONCOLOGY has grown in recent years as improved cancer survival rates have expanded the population of long-term survivors with heightened risk of cardiovascular disease (CVD) and drawn more attention to the need for preventive strategies and disease management. The toxic effects of cancer therapies on the heart and vascular system are significant contributors to morbidity and mortality, especially in patients who take anthracyclines or receive HER2-directed therapies but also for those treated with antiangiogenic therapies, tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors, targeted agents, and radiation (TABLE 1-2).

For many breast cancer survivors, the risk of death from CVD far exceeds the risk from their initial malignancy or recurrence. Research on cardiotoxicity has flourished, as seen in the pages of specialized cardio-oncology journals and the growing membership of the International Cardio-Oncology Society (IC-OS). Yet clinicians say a great deal about cardiovascular effects is still unknown. Against the rapid influx of novel anticancer agents, it can be difficult to fund studies of older drugs, and basic issues such as a uniform definition of cardiotoxicity, the utility of biomarkers, and the effectiveness of commonly used cardioprotective therapies remain unresolved.

“As soon as you start feeling like you’re getting familiar with one drug, there’s a whole new class of drugs coming out that have their own potential impact,” said Michael G. Fradley, MD, an associate professor of clinical medicine and medical director of the Thalheimer Center for Cardio-Oncology at Penn Medicine in Philadelphia, Pennsylvania. “As much as we have made progress with cardio-oncology, we are still really in a very early phase of the specialty, and there are probably still more questions than answers.”

Cardio-oncologists use assessment tools such as heart screenings, cardiac biomarker testing, and imaging via echocardiography. They can provide cardioprotective agents, such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins; treatments for heart failure (HF) and other conditions; and recommendations for exercise and dietary changes, dose modifications, and pauses in therapy.

EFFECTS ACROSS DRUG CLASSES

The cardiotoxic effects of anthracycline drugs such as daunorubicin and epirubicin have been a primary focus of cardio-oncological research for decades. They can cause cardiomyopathy, increased risk of HF, left-ventricular dysfunction (LVD), and arrhythmia. Although the use of anthracyclines in breast cancer care has decreased over the past 15 years, they are still used to treat patients with breast cancer as well as those with lymphoma, sarcoma, and many pediatric malignancies. Anthracycline-induced HF has been described as a leading comorbidity in survivors of childhood cancers.

The HER2-directed monoclonal antibody drug trastuzumab (Herceptin) has also been intensively investigated for cardiotoxic effects. It is associated with high rates of cardiac function declines and HF, with results from 1 retrospective study finding abnormal left ventricular ejection fraction (LVEF) decline in 43.9%...
(n = 179/408) of patients with breast cancer who had normal LVEF before treatment.² More than 6 years after treatment, patients with breast cancer who developed cardiotoxicity during trastuzumab therapy had significantly lower LVEF, global longitudinal strain (GLS), and peak oxygen consumption than those who had normal LVEF before treatment.⁵ More (n = 179/408) of patients with breast cancer who developed cardiotoxicity 5 years after treatment, patients with breast cancer who had normal LVEF before treatment. 5 More (n = 179/408) of patients with breast cancer who developed cardiotoxicity 5 years after treatment, patients with breast cancer who had normal LVEF before treatment. 5 More (n = 179/408) of patients with breast cancer who developed cardiotoxicity 5 years after treatment, patients with breast cancer who had normal LVEF before treatment. 5 More (n = 179/408) of patients with breast cancer who developed cardiotoxicity 5 years after treatment, patients with breast cancer who had normal LVEF before treatment. 5 More

TABLE. Cardio-Oncologic Outcomes Associated With Anticancer Therapies.¹,²

<table>
<thead>
<tr>
<th>Treatment class (agents)</th>
<th>Indications</th>
<th>Treatment-related toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyline chemotherapy (doxorubicin, epirubicin, daunorubicin, idarubicin)</td>
<td>Breast cancer, lymphoma, acute leukemia, sarcoma</td>
<td>Heart failure, asymptomatic LVSD, atrial and ventricular arrhythmias</td>
</tr>
<tr>
<td>HER2-targeted therapies (trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, neratinib, tucatinib)</td>
<td>HER2-positive breast cancer, HER2-positive gastric cancer</td>
<td>Heart failure, asymptomatic LVSD, hypertension</td>
</tr>
<tr>
<td>VEGF inhibitors</td>
<td>VEGF TKIs: renal cancer, hepatocellular cancer, thyroid cancer, colon cancer, sarcoma, GIST</td>
<td>Myocardial ischemia and infarction, QTc prolongation</td>
</tr>
<tr>
<td>Multitargeted kinase inhibitors: BCR-ABL TKIs (ponatinib, nilotinib, dasatinib, bosutinib)</td>
<td>Chronic myeloid leukemia</td>
<td></td>
</tr>
<tr>
<td>Proteasome inhibitors (carfilzomb, bortezomb, ixazomb)</td>
<td>Multiple myeloma</td>
<td>Heart failure, asymptomatic LVSD, hypertension, QTc prolongation</td>
</tr>
<tr>
<td>Combination RAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)</td>
<td>RAF-mutant melanoma</td>
<td>Heart failure and asymptomatic LVSD, hypertension, QTc prolongal</td>
</tr>
<tr>
<td>Androgen deprivation therapies</td>
<td>Prostate cancer, ER-positive breast cancer</td>
<td>Atherosclerosis, myocardial ischemia and infarction, diabetes mellitus, hypertension</td>
</tr>
<tr>
<td>Immune checkpoint inhibitors</td>
<td>Melanoma (metastatic and adjuvant), metastatic renal cancer, non-small cell lung cancer, small cell lung cancer, refractory Hodgkin lymphoma, metastatic triple-negative breast cancer, metastatic urothelial cancer, liver cancer, MMR-deficient cancer</td>
<td>Myocarditis (including fulminant myocarditis), pericarditis, noninflammatory heart failure, ventricular arrhythmias, AV block, acute coronary syndromes (including atherosclerotic plaque rupture and vasculitis)</td>
</tr>
</tbody>
</table>

AV, atriocentric; CV, cardiovascular; ER, estrogen receptor; GIST, gastrointestinal stromal tumor; GnRH, gonadotropin release hormone; LVSD, left ventricular systolic dysfunction; MMR, mismatch repair; PAOD, peripheral arterial occlusive disease; TKI, tyrosine kinase inhibitor.

*Associated with ponatinib.
*Associated with nilotinib and nilotinib.
*Associated with dasatinib.
*Associated with carfilzomb.
*Associated with vemurafenib and cobimetinib.

Antiangiogenic effects—the anti-VEGF therapy bevacizumab (Avastin) and TKIs such as sunitinib (Sutent) and sorafenib (Nexavar)—can cause hypertension and other effects. A meta-analysis of 77 studies of drugs targeting the VEGF-signaling pathway noted severe hypertension in 7.4% of patients, arterial thromboembolism in 1.8%, cardiac ischemia in 1.7%, and cardiac dysfunction in 2.3%.⁷

"The biggest issue you may encounter is obviously hypertension, which will lead to heart failure," said Daniel J. Lenihan, MD, professor of medicine and director of the Cardio-Oncology Center of Excellence at Washington University School of Medicine in St Louis, Missouri, and president of IC-OS. "It’s extremely common and depending on which drug you’re using it could [occur in] at least 50% of the patients or more."

Each TKI is associated with multiple potential cardiotoxic effects. Dasatinib (Sprycel), for example, is linked with an electrical disturbance in the heart muscle called QT prolongation, arterial stenosis, pericardial effusion, LVD, HF, and many other effects. Additionally, adverse effects (AEs) identified in patients receiving imatinib (Gleevec) include edema, pericardial effusion, peripheral edema, pulmonary edema, angina, and hypotension. The third-generation TKI ponatinib (Iclusig) has been described as “the most cardiotoxic FDA-approved TKI.” It has a high incidence of vascular occlusion events, hypertension, peripheral edema, left ventricular dysfunction, HF (including fatalities), and other AEs.

Recent studies have highlighted the cardiotoxicity of the TKI ibrutinib (Imbruvica). In a 3-arm chronic lymphocytic leukemia (CLL) trial (NCT01886872), atrial fibrillation occurred in 17% of patients in the ibrutinib group (n = 182), compared...
with 14% in the ibrutinib-rituximab group (n = 182) and 3% in the bendamustine-rituximab group (n = 183); grade 3 or higher hypertension rates were 29%, 34%, and 14%, respectively. The 2 ibrutinib arms were associated with a 7% rate of death during treatment or within 30 days after treatment cessation, compared with a 1% rate of death in the control arm.

**GRINDING THROUGH THE DETAILS**

The data from the CLL trial and other findings recently prompted a call for the FDA to require studies of lower-dose ibrutinib treatments, which may be as effective as the approved label dosages. Fradley and other cardio-oncologists note that trial results presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting showed that acalabrutinib (Calquence) causes fewer AEs, including CV effects, than ibrutinib in patients with previously treated CLL while offering similar efficacy. Regulators are aware of the cardiotoxicities of TKIs and other frequently used treatments, but incomplete understandings of the mechanisms of novel agents and the sheer volume of new therapies prevent systematic, prospective study of their effects, said Joerg Herrmann, MD, director of the cardio-oncology clinic at Mayo Clinic in Rochester, Minnesota. He noted that when trastuzumab was introduced clinicians had no idea it would have major impacts on the myocardium. In some cases, new drug molecules actually provide new insights on cardiovascular biology and pathology.

“A fair number of the drugs are being released into phase 1 and phase 2 trials without having the full characterization,” Herrmann said. “Some studies might have cardio-oncologist involvement, but it’s really hard to argue for that if you don’t even really fully know that molecule in terms of its AE profile. That is where the call for action would be, if there were something new; we could do it in terms of preclinical testing that is high throughput and reliable.”

With older drugs, pharmaceutical manufacturers have little incentive to fund new trials to study cardiotoxicities and may not want to advertise the drugs’ AEs, he said.

That said, investigators are continually working to identify the effects of specific drugs using registry data and meta-analyses. For example, a recent study used AE data from the FDA to investigate the effects of BRAF/MEK inhibitor combinations in melanoma patients. Compared with monotherapy, the combinations were associated with increased risk for HF (reporting odds ratio [ROR], 1.62; 95% CI, 1.14-2.30; P = .007), arterial hypertension (ROR, 1.75; 95% CI, 1.12-2.89; P = .02), and venous thromboembolism (ROR, 1.80; 95% CI, 1.12-2.89; P = .02). Results of the study also found higher rates of cardiovascular adverse events (CVAEs) for the combinations in a commercial claims database.

Immunotherapies are another area of interest. “Checkpoint inhibitors are associated with myocarditis, but they’re also associated with…

---

**FIGURE. Proposed Monitoring and Treatment for Patients Undergoing Potentially Cardiotoxic Anticancer Therapy**

- **Careful cardiac exam, ECG, baseline LVEF, cardiac biomarkers, lipid panel**
- **If high-risk features present, refer to cardio-oncology for optimal management**
- **LVEF <40%**
  - Cardioprotective therapy; consider first-line cancer therapy with cardio-oncology input and/or noncardiotoxic second-line cancer treatments
- **LVEF 40% to <50%**
  - Consider alternative noncardiotoxic treatments
- **LVEF >50%**
  - Start cancer treatment
- **Symptomatic HF**
  - Temporarily withhold cancer treatment
- **Absolute LVEF decrease of >20%**
  - Cardioprotective therapy; consider first-line cancer therapy with cardio-oncology input and/or noncardiotoxic second-line cancer treatments
- **Absolute LVEF decrease >10% to <50%**
  - Consider alternative noncardiotoxic treatments
- **Absolute LVEF decrease <10% to >50%**
  - Continue cancer treatment
- **Persistent reduced LVEF**
  - Periodic cardiac assessment, monitor LVEF, cardiac biomarkers
- **LVEF return to baseline**
  - Cardioprotective therapy; consider first-line cancer therapy with cardio-oncology input and/or noncardiotoxic second-line cancer treatments

ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction.
significant rhythm disturbances and worsening of atherosclerosis. Those conditions don’t really show up as a change in LV function necessarily; they show up as something else,” Lenihan said. In a meta-analysis of past clinical trials presented at 2021 ASCO, patients who received PD-1, PD-L1, and CTLA-4 inhibitors had increased relative risk (RR) of grade 3 to 5 CVAEs compared with those who received placebo or best supportive care (RR, 1.36; 95% CI, 1.06-1.73; \( P = .01 \)). However, analyses of individual AEs such as arrhythmia, cardiac arrest, and HF did not identify significant additional risks.

According to a consensus article from the European Society for Medical Oncology (ESMO), many other therapies with cardiovascular effects include protease inhibitors (carfilzomib; Kyprolis), mTOR inhibitors (everolimus; Afinitor), histone deacetylase inhibitors (vorinostat; Zolinza), endocrine therapies (tamoxifen, letrozole), chimeric antigen receptor T-cell therapies (tisagenlecleucel; Kymriah), and retinoids (tretinoin).

Many patients receive multiple types of therapies, further complicating cardiac care. Lenihan recently saw a patient with sarcoma who was treated first with doxorubicin, followed by pazopanib, pembrolizumab (Keytruda) for 2 years, and finally a drug combination, each of which may have affected her cardiovascular system in different ways.

“What is it that you’ve got to worry about in all those situations?” he asked. “It’s very complex and you have to grind through the details. A typical cardiologist response is, ‘Oh, the ejection fraction is in the normal range, so we don’t have any issues there, just move on.’ That’s not adequate. You have to look through the details of noninvasive test measurements, through the history of cancer therapy, their vital signs, demographics, and everything.”

### CARDIOPROTECTION REMAINS CONTROVERSIAL

Cardio-oncology care starts before cancer treatment with baseline measurement of LVEF and cardiac biomarkers, principally troponin levels but also natriuretic peptides such as B-type natriuretic peptide. Patients with preexisting CVD or risk factors may receive \( \beta \)-blockers, ACE inhibitors and angiotensin receptor blockers (ARBs). Statins are increasingly being given to prevent hyperlipidemia. But evidence for the benefit of cardioprotective drugs is mixed and their use remains controversial.

In the MANTICORE 101-Breast study (NCT01016886), the ACE inhibitor perindopril and \( \beta \)-blocker bisoprolol was found to protect against cancer therapy-related declines in LVEF in patients with HER2-positive early breast cancer who received trastuzumab, but trastuzumab-mediated left ventricular remodeling was not prevented.

In recent findings from the PRADA study (NCT01434134), the ARB candesartan administered during adjuvant breast cancer therapy did not prevent reduction in LVEF at 2 years but was associated with modest reduction in left ventricular end-diastolic volume and preserved GLS.\(^{15}\) The investigators concluded that a broadly administered cardioprotective approach may not be required in most patients with early breast cancer without preexisting CVD.

The \( \beta \)-blocker carvedilol is a frequently used cardioprotective agent. In the OVERCOME trial (NCT01110824), patients with certain hematological malignancies who received carvedilol and the ACE inhibitor enalapril showed a significant reduction in a combined end point of death, HF, or final LVEF less than 45% at 6 months compared with placebo.\(^{16}\) However, results of CECCY (NCT01724450), which was the largest trial in this class of drugs, did not prevent reduction in LVEF at 2 years associated with modest reduction in left ventricular end-diastolic volume and preserved GLS.\(^{15}\) The investigators concluded that a broadly administered cardioprotective approach may not be required in most patients with early breast cancer without preexisting CVD.

A log-rank test also showed a statistically significant difference in overall survival (OS) probability. The median OS with standard care therapy was 78.4 months (95% CI, 59.97 vs 98 months with management (95% CI, 89.7-106.2).

Results of a retrospective study of ponatinib for treatment of chronic myeloid leukemia found the incidence of CVAEs declined after investigators began making more cardio-oncology referrals, using a lower starting dose, and instituting early dose reductions.\(^{19}\) The TITAN study (NCT01621659) launched in 2012 is evaluating the effects of multidisciplinary team intervention on cardiotoxicity detection and management and on outcomes in patients with breast cancer or lymphoma.

Cardio-oncologists are confident their work makes a difference. Lenihan noted that CVD is the leading noncancer cause of death among cancer survivors and said cardio-oncological intervention is critical.

“If you simply manage somebody’s blood pressure and give them optimal cardia-based therapy, you have a huge impact. The difference between doing that and not doing it, basically it’s a life and death thing,” he said. “It’s very likely they will get all the way through that treatment and they will end up with normal heart function at the end. If you don’t do those things they may make it only halfway through their treatment.”

Among the challenges cardiologists face is the shifting definition of cardiotoxicity. In addition to debating questions such as...
Cardio-oncology

where to set the cutoff for abnormal LVEF during anthracycline and trastuzumab therapy, they are working to integrate the whole spectrum of newly discovered CV effects into their practices. Lenihan is a member of an international group that recently completed a broad literature review of cardiotoxicities—he hopes to see its proposed universal definition published soon.

Cardiovascular risk assessment is another area of active study. The European Society of Cardiology, in collaboration with IC-OS, last year published a set of risk-stratification tools, but cardiologists agree there is no generally accepted set of clear, standardized algorithms. They describe cardiac biomarkers as helpful in some scenarios and not others, and other potential useful technologies as not ready for clinical use.

“A lot still needs to be known in cardio-oncology, primarily in predicting who will develop cardiovascular disease and when. For predicting risk, in addition to genomics and precision medicine, artificial intelligence, particularly machine learning, is becoming of more interest in the field,” said Sherry-Ann Brown, MD, PhD, an assistant professor and director of cardio-oncology at Medical College of Wisconsin in Green Bay. Artificial intelligence tools are being developed for interpreting imaging and electrocardiograms, automating diagnosis, predicting HF risk, and other functions.

Fradley said cardiologists also need more information about the underlying mechanisms of cardiotoxicity, which are unclear for many drugs. For example, understanding how Bruton tyrosine kinase inhibitors cause atrial fibrillation and whether it differs from nontherapeutic atrial fibrillation could allow physicians to use a different treatment approach.

“If we can understand how or why cardiovascular disease happens, we’re going to be much better equipped at knowing how to treat it, or manage it, or even prevent it,” Fradley said. “It’s really drilling down from the observation that these things are happening to try to understand mechanistically why they’re happening.”

For a full list of references, see the article at OneLive.com.
TITAN final analysis data are not currently reported in the ERLEADA® Prescribing Information. The following TITAN primary analysis results are included in the ERLEADA® Prescribing Information:

**Median OS:**
- ERLEADA®: 17.3 months (95% CI: 16.2, 18.4)
- Placebo: 12.5 months (95% CI: 11.0, 13.8)
- **HR = 0.28; 95% CI: 0.23, 0.35; P < 0.0001**

**Median MFS:**
- ERLEADA®: 15.0 months
- Placebo: 7.7 months
- **HR = 0.78; 95% CI: 0.64, 0.96; P = 0.0053**

**Median DCR:**
- ERLEADA®: 16.4 months
- Placebo: 11.9 months
- **HR = 0.60; 95% CI: 0.46, 0.78; P < 0.0001**

**Cardiovascular Risk:**
- In a randomized study (TITAN) in patients with mCSPC, 1 in 4 patients treated with ERLEADA® and 1 in 8 patients treated with placebo died from a cerebrovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

**Seizure Events:**
- Across the SPARTAN and TITAN studies, 3 and 4 events.

**Laboratory Abnormalities:**
- Grade 3/4:
  - Hematology: Neutropenia ERLEADA® 17% (3%), placebo 11% (0%)
  - Gastrointestinal: Abnormal fat ERLEADA® 12% (2%), placebo 6% (1%)

**DRUG INTERACTIONS**
Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP3A4 or CYP3A inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, repeated dose escalation should be based on tolerability [See Dosage and Administration (2.2)].

**Effect of ERLEADA® on Other Drugs**
- CYP3A4, CYP2D6, and UGT1A1 Substrates — ERLEADA® is a weak inducer of P450-gene products (P-450), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

**INDICATIONS**
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

**IMPORTANT SAFETY INFORMATION**
- Metastatic castration-sensitive prostate cancer (mCSPC) treated with placebo. In a randomized study (TITAN) in patients with mCSPC, cerebrovascular and ischemic cardiovascular events, including transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies. In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® and 2.8% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

- Seizure Events — The most common adverse reactions (≥1%) that occurred more frequently in the ERLEADA®-treated patients (2% or more) from the randomized placebo-controlled clinical trial (TITAN and SPARTAN) were fatigue, asthenia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

**Laboratory Abnormalities** — All Grades (Grade 3-4)
- Hematology — In the TITAN study, white blood cell decreased ERLEADA® 2% (0.4%), placebo 10% (0.4%). In the SPARTAN study, anemia ERLEADA® 7% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.7%), placebo 29% (0.2%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).
- Chemistry — In the TITAN study, hyperglycemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study, hyperkalemia ERLEADA® 78% (2%), placebo 59% (1%).
- Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly diagnosed as macular or maculopapular. Adverse reactions of rash were seen with ERLEADA® ≥5% with placebo. Grade 3 rash (defined as covering ≥30% body surface area) was reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 10% of patients received topical corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

**Hypothyroidism** — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) for 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

**Hypersensitivity Reactions** — Hypersensitivity reactions, including anaphylactic shock, were reported with ERLEADA®. Rash is a common adverse reaction associated with administration of ERLEADA®. Rash is generally mild to moderate in severity and is characterized by erythematous papules or plaques. Rash may lead to discontinuation of treatment with ERLEADA®.

**Key Points**
- ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
  - Metastatic castration-sensitive prostate cancer (mCSPC)
  - Non-metastatic castration-resistant prostate cancer (nmCRPC)

- **Cardiovascular Risk:**
  - Cerebrovascular and ischemic cardiovascular events, including transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies. In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® and 2.8% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

- **Seizure Events —** The most common adverse reactions (≥1%) that occurred more frequently in the ERLEADA®-treated patients (2% or more) from the randomized placebo-controlled clinical trial (TITAN and SPARTAN) were fatigue, asthenia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

**Elevated TSH** — In a randomized study (SPARTAN), elevated TSH occurred in 25% of patients treated with ERLEADA® compared with 9% of patients treated with placebo (0.5%). Rash was commonly managed with oral antihistamines, topical corticosteroids, and 10% of patients received topical corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

**Hypothyroidism** — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) for 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.
Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE
ERLEADA is indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Cerebrovascular and Ischemic Cardiovascular Events
Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event.

In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA and 0.8% of patients treated with placebo (see Clinical Trial Experience). In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures
Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls
Falls occurred in patients receiving ERLEADA with increased frequency in the elderly (see Use in Specific Populations). Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure
Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Embryo-Fetal Toxicity
The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female (see Clinical Pharmacology (12.1) in Full Prescribing Information). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA (see Use in Specific Populations).

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:
- Cerebrovascular and Ischemic Cardiovascular Events (see Warnings and Precautions).
- Fractures (see Warnings and Precautions).
- Falls (see Warnings and Precautions).
- Seizure (see Warnings and Precautions).

Clinical Trial 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 most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were:
- Fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diaphoresis, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 16 months (range: 0.1 to 34 months) in patients who received placebo. Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (≥1%) were rash, fatigue, and hypertension.

Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN (mCSPC) and SPARTAN (nmCRPC) trials. All Grades is defined as any grade of severity. Grade 3-4 is defined as Grade 3 and Grade 4. The table also shows adverse reactions occurring in ≥2% of patients treated with ERLEADA and 2% or less of patients treated with placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients treated with ERLEADA and evaluate for loss of activity during treatment and for 3 months after the last dose of ERLEADA (see Use in Specific Populations).

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>47 (0.3%)</td>
<td>29 (0)</td>
<td>46 (0.5%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>70 (0.4%)</td>
<td>64 (0.5%)</td>
<td>7 (0.1%)</td>
<td>4 (0.3%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76 (0.1%)</td>
<td>46 (0)</td>
<td>40 (0.9%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>67 (2%)</td>
<td>49 (0.8%)</td>
<td>18 (0.4%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17 (0.4%)</td>
<td>15 (0.9)</td>
<td>2 (0.1%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>25 (0.5%)</td>
<td>6 (0.4%)</td>
<td>19 (0.3%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>28 (6)</td>
<td>9 (0.6)</td>
<td>19 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>6 (&lt;1)</td>
<td>0 (&lt;1)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>23 (0.4%)</td>
<td>16 (0)</td>
<td>7 (0.1%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (3)</td>
<td>16 (0.3)</td>
<td>2 (0.03%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

Additional adverse reactions of interest occurring in ≥2% but less than 10% of patients treated with ERLEADA included:
- diabetes (2%), acute kidney injury (2%), atrial fibrillation (2%), thyroid-stimulating hormone (TSH) elevation (2%), and deep vein thrombosis (2%).

Table 2 shows laboratory abnormalities that occurred in ≥15% of patients treated with ERLEADA and evaluate for loss of activity during treatment and for 3 months after the last dose of ERLEADA (see Use in Specific Populations).

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27 (0.4)</td>
<td>19 (0.3)</td>
<td>8 (0.15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>17 (3%)</td>
<td>12 (2)</td>
<td>5 (0.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values
ERLEADA® (apalutamide) tablets

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (≥2%) were fracture (8%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>ERLEADA N=524</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
<td>All Grades %</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatiguea,b</td>
<td>39 1 28 0.3</td>
<td>16 0 8 0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>25 5 6 0.3</td>
<td>12 1 9 0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rashc</td>
<td>16 2 9 0.8</td>
<td>12 3 7 0.8</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Falld</td>
<td>16 1 6 0.3</td>
<td>14 1 0 0</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreasede</td>
<td>25 14 20 12</td>
<td>14 0 9 0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>20 1 15 0.5</td>
<td>18 0 16 0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>16 0 16 0</td>
<td>12 0 12 0</td>
</tr>
</tbody>
</table>

a Includes fatigue and asthenia
b Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
c Includes rash, rash maculo-papular, generalized urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

d Includes appetite disorder, decreased appetite, early satiety, and hypophagia

Cushing's syndrome, hyperglycemia, hyponatremia, hypoalbuminemia, hypocalcemia, hypokalemia, hyperkalemia

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (6% versus 2% on placebo), and heart failure (2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70 0.4 64 0.5</td>
<td>47 0.3 29 0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47 0.3 29 0</td>
<td>41 2 21 2</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>47 0.3 29 0</td>
<td>41 2 21 2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76 0.1 46 0</td>
<td>70 2 59 1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>76 0.1 46 0</td>
<td>70 2 59 1</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values

Rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA treatment (8%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 58% experienced recurrence of rash upon reintroduction of ERLEADA.

Hyperthyroidism

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hyperthyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (see Drug Interactions).

Post-Marketing Experience

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

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability (see Dosage and Administration (2.2) in Full Prescribing Information). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity (see Clinical Pharmacology (12.3) in Full Prescribing Information).
ERLEADA® (apalutamide) tablets

P-gp, BCRP or OATP1B1 Substrates
Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/ OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1) in Full Prescribing Information]. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal development toxicology studies were not conducted with apalutamide.

Lactation
Risk Summary
The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential

Contraception
Males
Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. [see Use in Specific Populations].

Infertility
Males
Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in Full Prescribing Information].

Pediatric Use
Safety and effectiveness of ERLEADA in pediatric patients have not been established.

Geriatric Use
Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 to 74 years, and 40% were 75 years and over. No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (N=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 46% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE
There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

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

Cerebrovascular and Ischemic Cardiovascular Events
• Inform patients that ERLEADA has been associated with cerebrovascular and ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cerebrovascular or a cerebrovascular event occur [see Warnings and Precautions].

Falls and Fractures
• Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures
• Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions].

Rash
• Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions].

Dosage and Administration
• Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.

• Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

• Inform patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets [see Dosage and Administration (2.3) in Full Prescribing Information].

Embryo-Fetal Toxicity
• Inform patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions].

Infertility
• Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations].

Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00776
Manufactured for:
Janssen Products, LP
Horsham, PA 19044
© 2019 Janssen Pharmaceutical Companies
cp-50509v5
Fixed-Duration Venetoclax/Obinutuzumab Combo Improves Long-Term Outcomes for Patients With CLL

by JASON HARRIS

THE FIXED-DURATION ADMINISTRATION OF the BCL-2 inhibitor venetoclax (Venclexta) and the humanized anti-CD20 monoclonal antibody obinutuzumab (Gazyva) continued to confer a progression-free survival (PFS) advantage over chlorambucil plus obinutuzumab for patients with previously untreated chronic lymphocytic leukemia (CLL). Long-term follow-up data from the phase 3 CLL14 trial (NCT02242942) were presented during the European Hematology Association 2021 Virtual Congress.1

Investigators compared the combination of fixed-duration venetoclax and obinutuzumab vs obinutuzumab and chlorambucil in 432 treatment-naïve patients with CLL and coexisting medical conditions. Patients were evenly randomized to receive either regimen for twelve 28-day cycles.

The primary end point was investigator-assessed PFS. Secondary end points included independent review committee-assessed PFS, minimal residual disease (MRD) status, overall response rate (ORR), complete response (CR) or CR with incomplete hematologic recovery rates (CRI), overall survival (OS), duration of response, event-free survival, median time to next treatment (TTNT), and safety.

At a median follow-up of 52.4 months, the median PFS was not reached in the experimental arm vs 36.4 months in the chlorambucil/obinutuzumab arm (HR, 0.33; 95% CI, 0.25-0.45; P < .0001). The 4-year PFS rate was 74.0% for the 216 patients treated with venetoclax/obinutuzumab compared with 35.4% for 216 patients who received chlorambucil/obinutuzumab.

“With longer follow-up, we see that PFS is still favored in the venetoclax arm,” said lead author Othman Al-Sawaf, MD, a physician at the University Hospital of Cologne in Germany, in a virtual presentation of the data. “The majority of patients remain without disease progression even 3 years after completing their treatment.”

He added that the combination of venetoclax/obinutuzumab conferred a PFS benefit over chlorambucil/obinutuzumab irrespective of IGHV or TP53 mutation status (TABLE1). Mutation status was well balanced between treatment arms. For patients treated with venetoclax/obinutuzumab, 38% harbored an IGHV mutation and 12% of harbored a TP53 mutation. For patients treated with chlorambucil/obinutuzumab, 40% harbored and IGHV mutation and 12% harbored a TP53 mutation.

For patients with mutated IGHV, the median PFS with the venetoclax arm was not reached vs 54.5 months for the control arm. In those with unmutated IGHV, the median PFS was 57.3 months and 26.9 months, respectively.

For patients without TP53 aberrations, the median PFS was not reached in the experimental arm vs 38.9 months in the chlorambucil/obinutuzumab. For those whose disease harbored TP53 aberrations, the median PFS was 49.0 months and 20.8 months, respectively.

Baseline characteristics were well balanced between the 2 treatment arms. Overall, the median age was 71.5 years (range, 41-89), 43.5% had Binet stage C disease, the median total cumulative illness rating scale score was 8.3, and the median estimated creatinine clearance was 66.2 mL/min.

Most patients (66%) were in the intermediate tumor lysis syndrome category.
further analysis of mutational status, patients across arms reported 17p deletions (7.5%), 11q deletions (17.5%), 12 trisomy (18%), 13q deletions (35%), or no abnormalities (22%).

The median OS has not yet been reached in either arm (HR, 0.85; 95% CI, 0.54-1.35; \( P = .4929 \)); the 4-year OS rates were 85.3% for the venetoclax arm vs 83.1% for the control arm.

Additionally, the median TTNT was not reached in either treatment arm. The 4-year TTNT rate was 81.08% in the venetoclax/obinutuzumab arm compared with 59.9% in the chlorambucil/obinutuzumab arm. Thirty-five patients in the experimental arm had progressive disease, 17 of whom required antileukemic treatment, compared with 122 and 70 patients, respectively, in the control arm (HR, 0.46; 95% CI, 0.32-0.65; \( P < .0001 \)).

An assessment of MRD in peripheral blood 30 months after the end of treatment showed that 26.9% of patients in the experimental arm had undetectable MRD compared with 3.2% of patients in the chlorambucil/obinutuzumab arm. Al-Sawaf noted that patients in the control arm tended to lose MRD status after a median of 6 months vs 21 months with the venetoclax/obinutuzumab combination.

Regarding safety, there were no late onset or long-term toxicities with venetoclax/obinutuzumab in those patients evaluable for safety (n = 212, venetoclax/obinutuzumab; n = 214, chlorambucil/obinutuzumab). The most frequent grade 3 or higher adverse effects reported post treatment with venetoclax/obinutuzumab and chlorambucil/obinutuzumab were neutropenia (4.0% vs 1.9%, respectively), thrombocytopenia (0.5% vs 0%), anemia (1.5% vs 0.5%), febrile neutropenia 1.0% vs 0.5%), pneumonia (3.0% vs 1.4%), and infusion-related reaction (0% vs 0.5%).

There were 34 deaths in the experimental arm, 7 (20.5%) of which were related to CLL. Forty-one deaths occurred in the control arm, 16 (39%) of which were related to CLL. Al-Sawaf said most deaths on study were related to comorbid conditions.

“We are really able to mitigate the risk features of CLL by effectively controlling the disease,” Al-Sawaf said. “Therefore, our patients do not die of their cancer anymore, which is quite a substantial improvement.”

Investigators recorded secondary primary malignancies in 42 patients in the chlorambucil/obinutuzumab group vs 47 patients in the venetoclax/obinutuzumab group, which Al-Sawaf said was not statistically significant.

### TABLE. PFS Outcomes in CLL14 by Mutation Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Venetoclax/obinutuzumab</th>
<th>Chlorambucil/obinutuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TPS3 mutant</td>
<td>No TPS3 mutation</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>49.0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>IGHV mutant</td>
<td>No IGHV mutation</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>NR</td>
<td>57.3</td>
</tr>
</tbody>
</table>

NR, not reached; PFS, progression-free survival.

### FIGURE. Incidence of Aberrations, Mutations in CLL14 Trial

As part of the analysis of long-term follow-up data of the CLL14 trial (NCT02242942), investigators assessed the predictive and prognostic value of genomic aberrations, IGHV status, and mutations in TPS3, NOTCH1, SF3B1 and other candidate genes. The data were presented by Eugen Tausch, MD, an assistant doctor at the Clinic for Internal Medicine III at the Ulm University Hospital in Germany.

In total, 421 of 432 (97.4%) patients were evaluable at baseline, and prevalence of these aberrations is highlighted in the figure.
At a median follow-up of 52 months patients treated with venetoclax (Venclexta) and obinutuzumab (Gazyva) had a superior progression-free survival (PFS) compared with those treated with chlorambucil plus obinutuzumab in most genetic subgroups. Tausch highlighted that, in contrast to previously reported data, IGHV status is now considered a prognostic marker and is associated with shorter progression-free survival (PFS). This association was observed when stratified within treatment arms. In those treated with venetoclax/obinutuzumab, an HR of 2.14 (95% CI, 1.15-3.98) was reported for patients with no mutations vs those with mutations, and an HR of 3.07 (95% CI, 2.07-4.53) was reported for patients with either major TP53 mutations (variant allele frequency ≥ 10%) without del(17p) or those with TP53 minor mutations.

Patients with del(17p) had shorter overall survival (OS) in both the venetoclax (HR, 3.52; 95% CI, 1.53-8.17) and chlorambucil arms (HR, 5.67; 95% CI, 2.59-12.41). In terms of IGHV status, patients with no IGVH status treated with chlorambucil/obinutuzumab had the worst outcomes (HR, 2.83; 95% CI, 1.28-6.18).

In patients who relapsed after treatment, acquired mutations were analyzed. Among 88 patients who relapsed following treatment with chlorambucil/obinutuzumab, high-risk acquired mutations included BIRC3 (n = 5), ATM (n = 4), TP53 (n = 4), and SF3B1 (n = 3). Twenty-five patients relapsed after receiving venetoclax/obinutuzumab, and BIRC3, BAX, POT1, and TP53 mutations were reported acquired in 1 patient each. Of note, venetoclax-resistant mutations, including BCL2, BIM, BAX, BCL-XL, and MCL1, were not detected.

REFERENCE

More on OncLive.com

**Ghia on the Efficacy of Ibrutinib/Venetoclax in Patients With CLL**
Results from the phase 3 GLOW trial (NCT03462719) showed that the combination of ibrutinib (Imbruvica) and venetoclax (Venclexta) was very effective among elderly patients with chronic lymphocytic leukemia (CLL), according to Paola Ghia, MD, PhD. Many patients were able to achieve undetectable minimal residual disease, yielding deep responses in the peripheral blood and bone marrow at any time during treatment.

**Hillmen Highlights Acalabrutinib’s Tolerability Vs Ibrutinib in Previously Treated CLL**
The BTK inhibitor acalabrutinib (Calquence) demonstrated noninferiority to ibrutinib (Imbruvica) in terms of progression-free survival in patients with previously treated chronic lymphocytic leukemia (CLL) in the phase 3 ELEVATE-RR trial (NCT02477696). However, the agent was linked with reduced occurrences of common adverse effects, such as atrial fibrillation, according to Peter Hillmen, MD, PhD.
NOW APPROVED

FOTIVDA®
(tivozanib) capsules

Learn more at FOTIVDAhcp.com/nowapproved
Axi-Cel Induces Superior Survival, in R/R Follicular Lymphoma Vs Historical Controls

by COLLEEN MORETTI

**COMPARED WITH CURRENTLY AVAILABLE** therapies, treatment with axicabtagene ciloleucel (axi-cel; Yescarta) induced substantial improvements across clinical end points for patients with relapsed/refractory follicular lymphoma (R/R FL), according to results presented at the European Hematology Association 2021 Virtual Congress.1

Investigators sought to compare clinical outcomes from an updated 18-month analysis of the ZUMA-5 (NCT03105336) trial with a matched sample of patients from SCHOLAR-5, a generated external control cohort. Propensity score method was used to account for a broad set of prognostic covariates between the 2 cohorts of patients; and a total 85 patients from the SCHOLAR-5 cohort and 86 patients from ZUMA-5 were included in the analysis.

The common support data set included overall response rate (ORR), complete response (CR), overall survival (OS), progression-free survival (PFS), time to next treatment (TTNT), and duration of response (DOR).

The ORR was significantly higher for patients treated with axi-cel in the ZUMA-5 trial compared with those treated in SCHOLAR-5. Specifically, for patients treated with axi-cel the response rate was 94.2% vs 49.9% for those treated with other therapies (OR, 16.24; 94.2% vs 49.9% for those treated in SCHOLAR-5). The ORR was significantly higher compared with those enrolled to SCHOLAR-5, whereas it was 12.68 months (95% CI, 6.19-14.3) in the SCHOLAR-5 cohort with a reported 12-month OS rate of 92.9% (95% CI, 59.1%-99.0%) among 84 patients treated with the chimeric antigen receptor (CAR) T-cell therapy.2

We have to recall that the method [used to score] a complete remission within ZUMA-5 was by very strict criteria under central review, something which doesn’t really happen regularly in SCHOLAR-5,” Gribben explained. “[Therefore,] we can expect that the complete response rate might be downgraded [for SCHOLAR-5] if taken to a complete central review. Despite this, we see a significant difference in the complete remission rates. This was true for the [overall population] and true for a cohort of patients who had 3 or more prior lines of therapy in terms of overall responses as well as complete responses.”

STUDY DESIGN AND METHODOLOGY
ZUMA-5 is a prospective international study of axi-cel in patients with relapsed or refractory indolent non-Hodgkin lymphoma who have failed 2 or more prior lines of therapy. Primary analysis of outcomes for patients with relapsed or refractory follicular lymphoma demonstrated high rates of durable response—specifically, an ORR of 94% and a 12-month OS rate of 92.9% (95% CI, 59.1%-99.0%) among 84 patients treated with the chimeric antigen receptor (CAR) T-cell therapy.2

“We have to recall that the method [used to score] a complete remission within ZUMA-5 was by very strict criteria under central review, something which doesn’t really happen regularly in SCHOLAR-5,” Gribben explained. “[Therefore,] we can expect that the complete response rate might be downgraded [for SCHOLAR-5] if taken to a complete central review. Despite this, we see a significant difference in the complete remission rates. This was true for the [overall population] and true for a cohort of patients who had 3 or more prior lines of therapy in terms of overall responses as well as complete responses.”

Specifically, the reported odds ratios for ORR and CR rates for patients who received at least 3 prior lines of therapy included in SCHOLAR-5 compared with those enrolled to ZUMA-5 were 28.13 and 15.42, respectively. A median PFS was not reached (NR) in the cohort from ZUMA-5 (95% CI 23.52-NR), whereas it was 12.68 months (95% CI, 6.19-14.3) in the SCHOLAR-5 cohort with a reported HR of 0.30 favoring axi-cel (P < .001). “In the ZUMA-5 study, patients received a CT scan at month 1, at 3 months, and then every 3 months [after], and therefore PFS was very carefully monitored, much more rigorously than it would be in the real-world setting,” Gribben noted. “Despite this difference in assessment, the PFS was significantly longer in ZUMA-5 compared with SCHOLAR-5 and findings were consistent in the subgroup of patients who [had] 3 or more prior lines of therapy [HR, 0.20].”

TTNT was NR (95% CI, not estimable [NE]-NE) in the ZUMA-5 cohort compared with 14.43 months (95% CI, 6.24-25.76) for those in the SCHOLAR-5 cohort with a reported HR of 0.42 (P < .001). Additionally, the OS was significantly longer in ZUMA-5 with a reported 58% reduction in the risk of death. The median OS was NR (95% CI, 31.6-NE) in the ZUMA-5 cohort vs 59.8 months (95% CI, 21.9-NE) in the SCHOLAR-5 cohort (P = 0.0125).

“The substantial overall survival benefit seen in this study suggests that axi-cel addresses an important unmet medical need for patients with relapsed/refractory follicular lymphoma patients,” Gribben said. He also noted that these findings were maintained across 5 prespecified sensitivity analyses and no differences were found when this methodology was used.

“These data certainly support that axi-cel represents a significant improvement in treatment options for patients with relapsed/refractory follicular lymphoma,” Gribben concluded.


“The substantial overall survival benefit seen in this study suggests that axi-cel addresses an important unmet medical need for patients with relapsed/refractory follicular lymphoma patients,” Gribben said. He also noted that these findings were maintained across 5 prespecified sensitivity analyses and no differences were found when this methodology was used.

“These data certainly support that axi-cel represents a significant improvement in treatment options for patients with relapsed/refractory follicular lymphoma,” Gribben concluded.

John Gribben, MD, DSc, FRCPath, FMed Sci
trial,” he noted. Gribben went on to explain that experimental treatment options were commonly used in later lines of treatment.

Gribben noted that propensity score weighting was used to overcome bias and difficulty in the interpretation of data because of cross-study comparisons of a retrospective study vs a prospective clinical trial.

Following weighting, all baseline characteristics between cohorts were balanced except for ECOG performance status. A majority of patients in SCHOLAR-5 (71%) had an ECOG performance status of 1 compared with those in ZUMA-5 (40.7%).

After propensity score weighting, the median ages for the ZUMA-5 and SCHOLAR-5 cohorts were 62 (range, 34-79) and 61 years (range, 36-89), respectively. Patients in ZUMA-5 had a median of 3.5 prior lines of therapy compared with a median of 3.53 for those in SCHOLAR-5. The mean sizes of the largest lymph node were 5.2 cm and 4.93 cm, respectively.

“After applying propensity score methods, axi-cel demonstrated a substantial improvement in all clinical end points in the ZUMA-5 clinical trial compared with SCHOLAR-5,” Gribben concluded, adding that the deep and durable treatment effect of axi-cel supports its use for this patient population.

REFERENCES

Naratuximab Emtansine/Rituximab Combo Elicits Clinical Activity in Relapsed/Refractory DLBCL
by LISA ASTOR

THE COMBINATION OF NARATUXIMAB emtansine (Nara; Debio 1562, formerly IMGN529) and rituximab (Rituxan) yielded deep responses for a median duration that was not yet reached in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), according to findings from a phase 2 trial (NCT02564744) presented during the European Hematology Association 2021 Virtual Congress.1

Moshe Yair Levy, MD, director of hematologic malignancies research at Texas Oncology-Baylor Charles A. Sammons Cancer Center in Dallas, suggested during the presentation that the combination regimen could be a new treatment option for patients with relapsed/refractory DLBCL, including frail and heavily pretreated patients.

Naratuximab emtansine is an antibody-drug conjugate (ADC) comprised of the humanized anti-CD37 antibody K7153A, which is conjugated through a thioether-based linker to the cytotoxic maytansinoid DM1. CD37 is a surface marker on B lymphocytes and is highly expressed in non-Hodgkin lymphomas (NHLs). “It’s also a sizable cell surface antigen, which lends itself well to an antibody-drug construct,” Levy noted.

“[Naratuximab] is the most advanced CD37-targeted antibody-drug conjugate in clinical development in diffuse large B-cell lymphoma.”

Of the 76 evaluable patients with DLBCL in the phase 2 trial, the objective response rate (ORR) was 44.7% and complete responses (CRs) were reported in 31.6% of patients. The median duration of response was not reached (95% CI, 9-18) after a median of 15 months of follow-up. Sixty-six percent of responders had a response lasting more than a year.

DESIGNING AN ADAPTIVE TRIAL
Previously in a phase 1 study (NCT01534715), naratuximab emtansine monotherapy showed a manageable safety profile and an ORR of 22% in patients with DLBCL.2

“[Investigators] found that if you coadminister this ADC with rituximab, you’re actually going to get more internalization of the CD37 monoclonal antibody, [and therefore] more payload [will be] delivered to your target cells. This led to this phase 2 study,” Levy said.

The open-label, multicenter phase 2 study had an adaptive design.1 The safety run-in in part 1 included patients with relapsed/refractory NHL, including 9 with DLBCL and 8 with other NHLs. Patients were treated with 0.7 mg/kg naratuximab emtansine every 3 weeks on day 1 of the cycle followed by rituximab 375 mg/m². This was followed by a run-in expansion with 2 cohorts including 8 patients with relapsed/refractory DLBCL in cohort 1 and 12 patients with other NHLs in cohort 2, all treated at the same schedule.

In part 2 of the study, only patients with DLBCL were enrolled; they were treated with different dose schedules in the 2 cohorts. In cohort A, 33 patients were treated on the same every 3-week schedule; in cohort B, 30 patients were treated on a weekly schedule with 0.4 mg/kg naratuximab emtansine on day 1 of the 3-week cycle as well as on days 8 and 15 at 0.2 mg/kg followed by rituximab 375 mg/m² on day 1 of each cycle.

ORR by Lugano classification was the primary end point, and other trial objectives were safety in terms of treatment-emergent
adverse effects (TEAEs), changes in laboratory tests, and changes in vital signs.

The overall trial enrolled patients with an ECOG performance status of 0 to 2 who had received 1 to 6 prior lines of treatment. Those with central nervous system lymphomas were excluded, but patients with double- or triple-hit lymphoma, bulky disease, or transformed lymphoma were eligible for enrollment. Additionally, there were no limits on life expectancy in the trial, so it was “a very inclusive type of study,” according to Levy.

In part 1, patients were required to have received a confirmed diagnosis of relapsed/refractory NHL, including DLBCL, follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma. Prior allogeneic stem cell transplant was not allowed. Then in part 2, patients were required to have received a confirmed diagnosis of relapsed/refractory DLBCL and ineligibility for stem cell transplant.

Patients in the study ranged from 29 to 88 years old and were mostly male with Ann Arbor stage III or IV disease and extra-nodal disease involvement. In patients with DLBCL treated with the every-3-week schedule, the median number of prior therapies was 2. Among patients treated with the weekly regimen, the median number of prior therapies was 1. Forty percent of patients were refractory to their last treatment in the every-3-week group, and 13.3% were refractory in the weekly group.

As of data cutoff on January 13, 2021, 36.0% of patients with DLBCL treated every 3 weeks in cohort 2. After 6 cycles, patients could request an extension.

The median number of treatment cycles was 3 (range, 1-38) in cohort A, 5.5 (range, 1-30) in cohort B, and 7 (range, 1-52) in cohort 2. Discontinuation of both drugs—as protocol designated that if naratuximab emtansine was to be discontinued, rituximab would be as well—was primarily due to progressive disease across the study groups; adverse events leading to death were reported in 2 patients.

Further follow-up data showed that the ORR was 50% for patients in cohort A and CRs were observed in 43.3%. In cohort B, the ORR was also 50% and CRs were reported in 33.3% (FIGURE). Among patients with nonbulky DLBCL, the ORR was 50.8%. Patients treated in the third line or beyond who were not primary refractory showed an ORR of 46.4% and a CR rate of 32.1%.

SAFETY

Grade 3/4 TEAEs were mostly hematologic and manageable, including most commonly neutropenia (54.0%), leukopenia (19.0%), lymphopenia (17.0%), and thrombocytopenia (12.0%). Additionally, 3 grade 3 or higher liver TEAEs and 2 grade 3 or higher nonserious neuropathy cases were reported.

Levy noted that no granulocyte colony stimulating factor was mandated in the trial. “If it was, we probably would have seen a difference in the toxicity profile from the complication of cytopenias,” he said.

Grade 5 TEAEs were reported in 10 patients. Common serious adverse events included pneumonia/lung infection (5.0%), febrile neutropenia (4.0%), and general physical health deterioration (3.0%). Eight patients discontinued treatment due to a TEAE, and 6 patients required a dose reduction.

“[This] speaks to just how fragile this group of patients was, and the rather liberal inclusion criteria that allowed people irrespective of the amount of time we thought they had left,” Levy said. “This is, in my viewpoint, very exciting therapy. Clearly we have a need for another target in diffuse large B-cell lymphoma, and this certainly seems to compare quite favorably to other ADCs that we have seen in the space.”

REFERENCES


Investigators Look to Enhance Response With Novel Triplet in CLL

by DENISE MYSHKO

INVESTIGATORS OF THE PHASE 3
ULTRA-V trial (NCT03801525) are looking to leverage the synergistic capabilities of venetoclax (Venclexta) for patients with chronic lymphocytic leukemia (CLL) with the addition of the U2 regimen of umbralisib (Ukoniq)1 in combination with venetoclax.

Venetoclax, a highly selective BCL-2 inhibitor, is approved by the FDA for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL).2 The agent has demonstrated efficacy as both a monotherapy and in combination with anti-CD20 monoclonal antibodies such as obinutuzumab (Gazyva) or PI3K inhibitors such as duvelisib (Copiktra).3

"Venetoclax is a very potent drug and adds a lot of synergy to B-cell receptor antagonists," said Richard R. Furman, MD, director of the CLL Research Center at Weill Cornell Medicine in New York, New York. "We’ve had great success with ibrutinib (Imbruvica) plus venetoclax, but we had a lot of issues with combining the 2 in terms of drug-drug interaction and adverse events such as diarrhea, thrombocytopenia, and neutropenia," said Furman, who is also a member of the Lymphoma/Myeloma Service in the Division of Hematology/Oncology. "B-cell receptor antagonists and venetoclax would be the most potent tools we have for CLL treatment. The goal is to identify the best partner.”

TAKING STOCK OF SYNERGY IN THE LANDSCAPE
Building on the success of venetoclax with both anti-CD20 therapies and PI3Kd inhibitors, investigators turned their attention to 2 agents that have previously demonstrated efficacy for patients with CLL.

Umbralisib, an inhibitor of PI3K, was approved by the FDA in February for the treatment of adult patients with relapsed or refractory follicular lymphoma after at least 3 prior lines of systemic therapy. Further, the indication extends to adult patients with relapsed or refractory marginal zone lymphoma who have received at least 1 prior anti-CD20-based regimen.4

The second agent, ublituximab, is an investigational glycoengineered anti-CD20 monoclonal antibody. In March 2021, developer TG Therapeutics completed a rolling submission to the FDA for the combination of ublituximab and umbralisib as a treatment for patients with CLL. In May 2021, the FDA accepted the biologics license application for the combination therapy and is expected to decide on the application by March 25, 2022.5,6

The application for the U2 regimen is supported by data from the UNITY-CLL trial (NCT02612311), a global phase 3 study evaluating U2 compared with obinutuzumab plus chlorambucil in patients with previously untreated and relapsed/refractory CLL. Investigators presented data from this trial at the 2020 Annual Meeting of the American Society of Hematology (ASH).7 Approximately 420 participants were enrolled to 2 combination arms; 60% of patients were treatment-naïve and 40% had relapsed or refractory disease. The primary end point was superior progression-free survival (PFS). At a median follow-up of 36.7 months, the median PFS in the U2 treatment group (n = 210) was 31.9 months (95% CI, 28.2-35.8) compared with 17.9 months (95% CI, 16.1-22.6) in the obinutuzumab/chlorambucil treatment group (n = 211). The hazard ratio was 0.546 (95% CI, 0.414-0.720; P < .0001). The 2-year PFS rates were 60.8% and 40.4%, respectively. Investigators reported that responses were durable with U2 with 62% of patients maintaining a response at 2 years. Further, the disease control rate was 93% with U2.

The combination represents an opportunity to fulfill an unmet need for patients with CLL who are not ideal candidates for or who are refractory to treatment with Bruton tyrosine kinase (BTK) inhibitors. The combination of U2 plus venetoclax demonstrated promising efficacy in early data from the phase 1 study of the triplet regimen. In updated data from ASH 2020, the therapeutic regimen was well-tolerated and highly effective among evaluable patients after 3 (n = 39), 7 (n = 31), and 12 cycles (n = 27) of treatment.7

The U2 debulking regimen took place for 3 cycles, after which the overall response rate (ORR) was 77%. After cycle 7, treatment

FIGURE. Umbralisib and Ublituximab Combination With Venetoclax in CLL

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>Experimental arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adequate organ system function</td>
<td>umbralisib + venetoclax</td>
<td>umbralisib</td>
</tr>
<tr>
<td>• No prior exposure to PI3K inhibitor or venetoclax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients with autologous hematologic stem cell transplant within 6 months of study entry are excluded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients with active hepatitis B or C are excluded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse effects; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PFS, progression-free survival.
with U2 plus venetoclax resulted in a 100% ORR; after cycle 12, the ORR remained 100% with a 41% complete response rate and a 59% partial response rate.

Moreover, in the 27 patients evaluable after cycle 12, undetectable minimal residual disease (MRD) in the peripheral blood was observed in 96% of patients, and undetectable MRD (<.01%) in the bone marrow was observed in 77% of patients.7

Of note, in patients with BTK-refractory disease (n = 13), the ORR was 64% following debulking at the end of cycle 3 and 74% for all patients who received prior BTK inhibitors (n = 25).

Investigators concluded that based on these results the triplet regimen offers an effective 12-month chemotherapy-free option for this patient population.

DETAILED INFORMATION OF THE ULTRA-V TRIAL

Building on the design of the phase 1/2 study, the phase 3 ULTRA-V trial will consist of an induction and debulking regimen of ublituximab infusions in combination with daily umbralisib for 3 cycles. Starting with cycle 4, consolidation therapy with venetoclax begins and is added at the standard 5-week ramp-up phase for patients with CLL starting at 20 mg and increasing to 50, 100, 200, and 400 mg weekly. Treatment with 900-mg ublituximab infusions continues on day 1 of cycles 4, 5, and 6; daily umbralisib continues through cycle 15. Extended therapy is continued after cycle 15 for patients with detectable MRD.1,7

The study is expected to enroll approximately 700 treatment-naive or previously treated patients with CLL. In order to be eligible for enrollment, patients should have no prior exposure to a PI3K inhibitor or venetoclax, and patients with autologous hematologic stem cell transplant within 6 months of study entry or have active hepatitis B or C.

Patients will be randomized 1:1 to either the U2 plus venetoclax time-limited regimen or to U2 alone, which will be administered until disease progression. The primary end point is PFS, and secondary end points include safety and overall response rate (FIGURE1).

CONTINUING RESEARCH

In addition to the phase 3 trial, the ongoing, single-arm phase 2 portion of the ULTRA-V trial is evaluating the same triplet regimen in patients with CLL. The trial has completed patient enrollment with approximately 165 participants with newly diagnosed or relapsed/refractory CLL, including those whose disease is BTK refractory. The primary end points of the study are ORR and complete response at 12 months.

The U2 combination is also under investigation with U2 for patients with B-cell malignancies treated with the combination of TG-1701 and U2 was 82.3% with a 23.5% complete response rate and a 52.9% partial response rate.8

Of note, with a median follow-up of 8.6 months, the ORR for patients with CLL (n = 19) was 100% with TG-1701 alone administered at the 300-mg dosage and 95% with TG-1701 monotherapy administered at the 200-mg dosage. Investigators noted that the maximum-tolerated dose was not determined at the time of presentation.8

REFERENCES


**Indication:** PIQRAY® (alpelisib) tablets is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer (aBC or MBC) as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

**Important Safety Information**
PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components.

**Severe Hypersensitivity:** Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of grade 3 and 4 hypersensitivity reactions was 0.7%. Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

**Severe Cutaneous Adverse Reactions (SCARs):** SCARs including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY. In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of patients, respectively. DRESS was reported in patients in the postmarketing setting. If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend alpelisib (PIQRAY®) + fulvestrant as a Category 1 preferred option after using a CDK4/6 inhibitor + ET1 of HR+/HER2- aBC patients have a PIK3CA mutation 3~40%**

Patients with a PIK3CA mutation face a poor prognosis

Test patients for PIK3CA mutations at HR+/HER2- MBC diagnosis to be ready to treat at progression

PIK3CA mutation testing is available to eligible patients at no cost.

†Following progression on or after an endocrine-based regimen.

‡Terms and conditions may apply.

To learn more, visit www.HCP-PIQRAY.com

**Don't miss the driver of her disease—it can make her treatment clear**
Patients with a PIK3CA mutation face a poor prognosis\(^2\)

\(~40\%~ of \text{HR+/HER2- aBC patients have a PIK3CA mutation}^3\)

PIQRAY + fulvestrant nearly doubled mPFS in patients with a PIK3CA driver mutation\(^4\)

PFS\(^4,6\)

SOLAR-1 is a double-blind, placebo-controlled, multicenter phase 3 study in men and postmenopausal women with HR+/HER2- advanced or metastatic breast cancer with or without a PIK3CA mutation whose disease had progressed or recurred on or after aromatase inhibitor-based treatment (N=572). In the PIK3CA mutation cohort (n=341), patients were randomized 1:1 to receive PIQRAY 300-mg tablets orally once daily + fulvestrant 500 mg IM\(^*\) or placebo + fulvestrant 500 mg IM.\(^*\) The primary endpoint was PFS in patients with a PIK3CA mutation by investigator assessment per RECIST v1.1.

\(^*\)Fulvestrant given on day 1 and day 15 of the first 28-day cycle, then day 1 of subsequent 28-day cycles.

~2x mPFS

Number of subjects still at risk:

\[
\begin{array}{cccccccccccccccc}
\text{PIQRAY + fulvestrant} & 169 & 145 & 123 & 97 & 85 & 75 & 62 & 50 & 39 & 30 & 17 & 14 & 5 & 3 & 1 & 1 & 0 \\
\text{Placebo + fulvestrant} & 172 & 120 & 89 & 88 & 67 & 54 & 46 & 37 & 29 & 20 & 14 & 9 & 3 & 2 & 0 & 0 & 0 \\
\end{array}
\]

\[\text{HR}=0.65 \quad (95\% \text{ CI, } 0.50-0.85) \quad P=.0013\]

Test patients for PIK3CA mutations at HR+/HER2- MBC diagnosis to be ready to treat at progression\(^{4,6}\)

PIK3CA mutation testing is available to eligible patients at no cost.\(^1\)

See available resources at hcp-piqray.com/PIK3CAtesting

Important Safety Information (cont)

Severe Cutaneous Adverse Reactions (SCARs) (cont): If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCARs during PIQRAY treatment. If it is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment.

Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
Important Safety Information (cont)

**Hyperglycemia:** Severe hyperglycemia, including ketoacidosis, can occur in patients treated with PIQRAY® (alpelisib) tablets. Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG >250-500 mg/dL) and grade 4 (FPG >500 mg/dL) hyperglycemia were reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY.

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment with PIQRAY, monitor fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. If a patient experiences hyperglycemia after initiating treatment with PIQRAY, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a health care practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes.

The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified diabetic treatment. Closely monitor patients with diabetes.

Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients of the signs and symptoms of hyperglycemia (eg, excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss).

**Pneumonitis:** Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, can occur in patients treated with PIQRAY. Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis. Consider a diagnosis of noninfectious pneumonitis in patients presenting with nonspecific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue PIQRAY in all patients with confirmed pneumonitis. Advise patients to immediately report new or worsening respiratory symptoms.

**Diarrhea:** Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n=19) of patients. Based on the severity of the diarrhea, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their health care provider if diarrhea occurs while taking PIQRAY.
**Important Safety Information (cont)**

**Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose. Refer to the full Prescribing Information of fulvestrant for pregnancy and contraception information.

**The most common adverse reactions (all grades, incidence ≥20%)** were diarrhea (58%), rash (52%), nausea (45%), fatigue (42%), decreased appetite (36%), stomatitis (30%), vomiting (27%), weight decreased (27%), and alopecia (20%). The most common grade 3/4 adverse reactions (incidence ≥2%) were rash (20%), diarrhea (7%), fatigue (5%), weight decreased (3.9%), nausea (2.5%), stomatitis (2.5%), and mucosal inflammation (2.1%).

**The most common laboratory abnormalities (all grades, incidence ≥20%)** were glucose increased (79%), creatinine increased (67%), lymphocyte count decreased (52%), gamma-glutamyl transferase (GGT) increased (52%), alanine aminotransferase (ALT) increased (44%), hemoglobin decreased (42%), lipase increased (42%), calcium decreased (27%), glucose decreased (26%), and activated partial thromboplastin time (aPTT) prolonged (21%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were glucose increased (39%), GGT increased (11%), lymphocyte count decreased (8%), lipase increased (7%), and potassium decreased (6%).

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

**References:**

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
PIQRAY® (alpelisib) tablets, for oral use

Initial U.S. Approval: 2019

1 INDICATIONS AND USAGE
PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

4 CONTRAINDICATIONS
PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Severe Hypersensitivity
Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia.

The incidence of Grade 3 and 4 hypersensitivity reactions was 0.7% [see Adverse Reactions (6)].

Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

5.2 Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY.

In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of the patients, respectively [see Adverse Reactions (6.1)]. Drug reaction with eosinophilia and systemic symptoms (DRESS) was reported in patients treated with PIQRAY in the postmarketing setting [see Adverse Reactions (6.2)].

If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous severe cutaneous adverse reactions during PIQRAY treatment.

If a SCAR is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment as described in Table 2 [see Dosage and Administration (2.3) in the full prescribing information].

Advise patients of the signs and symptoms of SCARs (e.g., a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

5.3 Hyperglycemia
Severe hyperglycemia, including ketoadiposis, can occur in patients treated with PIQRAY. Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FFG > 250 to 500 mg/dL) and Grade 4 (FFG > 500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoadiposis was reported in 0.7% of patients (n = 2) treated with PIQRAY.

Among the patients who experienced Grade 2 (FFG 160 to 250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range, 5 to 517 days).

In the 187 patients with hyperglycemia, 87% (163/187) were managed with anti-diabetic medication, and 76% (142/187) reported use of metformin as a single agent or in combination with other anti-diabetic medication (i.e., insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas). In patients with Grade ≥ 2 hyperglycemia with at least 1 grade improvement (n = 153), median time to improvement from the first event was 8 days (range, 2 to 65 days).

In all patients with elevated FPG who continued fulvestrant treatment after discontinuing PIQRAY (n = 54), 96% (n = 52) of patients had FPG levels that returned to baseline.

Before initiating treatment with PIQRAY, test fasting plasma glucose (FFG), HbA1c, and optimize blood glucose. After initiating treatment with PIQRAY, monitor fasting glucose (FFG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated.

If a patient experiences hyperglycemia after initiating treatment with PIQRAY, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. During treatment with anti-diabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a healthcare practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes.

The safety of PIQRAY in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of Type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified diabetic treatment. Closely monitor patients with diabetes.

Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 3 [see Dosage and Administration (2.3) in the full prescribing information].

Advise patients of the signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss).

5.4 Pneumonitis
Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, can occur in patients treated with PIQRAY.

Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis. Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue PIQRAY in all patients with confirmed pneumonitis.

Advise patients to immediately report new or worsening respiratory symptoms.

5.5 Diarrhea
Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n = 19) of patients. Among patients with Grade 2 or 3 diarrhea (n = 71), the median time to onset was 46 days (range, 1 to 442 days).

Dose reductions of PIQRAY were required in 6% of patients and 2.8% of patients permanently discontinued PIQRAY due to diarrhea. In the 164 patients that experienced diarrhea, anti-diarrheal medications (e.g., loperamide) were required to manage symptoms in 63% (104/164) of these patients.

Based on the severity of the diarrhea, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 4 [see Dosage and Administration (2.3) in the full prescribing information].

Advise patients to start anti-diarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs while taking PIQRAY.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:

• Severe Hypersensitivity [see Warnings and Precautions (5.1)]
• Severe Cutaneous Adverse Reactions [see Warnings and Precautions (5.2)]
• Hyperglycemia [see Warnings and Precautions (5.3)]
• Pneumonitis [see Warnings and Precautions (5.4)]
• Diarrhea [see Warnings and Precautions (5.5)]

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

The safety of PIQRAY was evaluated in a randomized, double-blind, placebo-controlled trial (SOLAR-1) in 571 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled into two cohorts, with or without a PIK3CA mutation [see Clinical Studies (14) in the full prescribing information].
Patients received either PIQRAY 300 mg plus fulvestrant (n = 284) or placebo plus fulvestrant (n = 287). Fulvestrant 500 mg was administered intramuscularly on Cycle 1, Day 1 and 15, and then at Day 1 of each 28-day cycle during treatment phase.

Two patients (0.7%) died while on treatment with PIQRAY plus fulvestrant due to causes other than the underlying malignancy. Causes of death included one cardio-respiratory arrest and one second primary malignancy. Neither was suspected to be related to study treatment.

Serious adverse reactions occurred in 35% of patients receiving PIQRAY plus fulvestrant. Serious adverse reactions in > 2% of patients receiving PIQRAY plus fulvestrant included hyperglycemia (10%), rash (3.5%), diarrhea (2.8%), acute kidney injury (2.5%), abdominal pain (2.1%), and anemia (2.1%).

Osteonecrosis of the jaw (ONJ) was reported in 4.2% of patients (12/284) in the PIQRAY plus fulvestrant arm compared to 1.4% of patients (4/287) in the placebo arm. All patients experiencing ONJ had prior or concomitant bisphosphonates or RANK-ligand inhibitor administration.

Among patients receiving PIQRAY plus fulvestrant, 4.6% permanently discontinued both PIQRAY and fulvestrant and 21% permanently discontinued PIQRAY alone, due to ARs. The most frequent ARs leading to treatment discontinuation of PIQRAY in > 2% patients receiving PIQRAY plus fulvestrant were hyperglycemia (6%), rash (4.2%), diarrhea (2.8%), and fatigue (2.5%). Dose reductions due to ARs occurred in 55% of patients receiving PIQRAY plus fulvestrant. The most frequent ARs leading to dose reduction in > 2% patients receiving PIQRAY plus fulvestrant were hyperglycemia (29%), rash (9%), diarrhea (6%), stomatitis (3.5%), and mucosal inflammation (2.1%).

The most common adverse reactions, including laboratory abnormalities (all grades, incidence ≥ 20%) were glucose increased, creatinine increased, diarrhea, rash, lymphocyte count decreased, gamma glutamyl transferase (GGT) increased, nausea, alanine aminotransferase (ALT) increased, fatigue, hemoglobin decreased, lipase increased, decreased appetite, stomatitis, vomiting, weight decreased, calcium decreased, glucose decreased, activated partial thromboplastin time (aPTT) prolonged, and alopecia.

Adverse reactions and laboratory abnormalities are listed in Table 6 and Table 7, respectively.

### Table 6: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher than Placebo Arm in SOLAR-1 (All Grades)

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>PIQRAY plus fulvestrant N = 284</th>
<th>Placebo plus fulvestrant N = 287</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58</td>
<td>7*</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>2.5*</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>30</td>
<td>2.5*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27</td>
<td>0.7*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>1.4*</td>
</tr>
<tr>
<td>Dyspepsis</td>
<td>11</td>
<td>0*</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>42</td>
<td>5*</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19</td>
<td>2.1*</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15</td>
<td>0*</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0.7</td>
</tr>
<tr>
<td>Mucosal dryness</td>
<td>12</td>
<td>0.4*</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10</td>
<td>0.7*</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>27</td>
<td>3.9*</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>36</td>
<td>0.7*</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>18</td>
<td>0.4*</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>0.7*</td>
</tr>
</tbody>
</table>

### Table 7: Laboratory Abnormalities Occurring in ≥ 10% of Patients in SOLAR-1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>PIQRAY plus fulvestrant N = 284</th>
<th>Placebo plus fulvestrant N = 287</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>42</td>
<td>4.2*</td>
</tr>
<tr>
<td>Activated Partial Thromboplastin Time (aPTT) prolonged</td>
<td>21</td>
<td>0.7*</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Biochemical parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>79</td>
<td>39</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>67</td>
<td>2.8*</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase (GGT) increased</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT) increased</td>
<td>44</td>
<td>3.5</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>Calcium (corrected) decreased</td>
<td>27</td>
<td>2.1</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>26</td>
<td>0.4</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>14</td>
<td>0*</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>11</td>
<td>0.4*</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PIQRAY. 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.

**Skin and subcutaneous tissue disorders**: Drug reaction with eosinophilia and systemic symptoms (DRESS).
7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on PIQRAY
CYP3A4 Inducer
Coadministration of PIQRAY with a strong CYP3A4 inducer may decrease alpelisib concentration [see Clinical Pharmacology (12.3) in the full prescribing information], which may decrease alpelisib activity. Avoid coadministration of PIQRAY with strong CYP3A4 inducers.

Breast Cancer Resistance Protein Inhibitors
Coadministration of PIQRAY with a breast cancer resistance protein (BCRP) inhibitor may increase alpelisib concentration [see Clinical Pharmacology (12.3) in the full prescribing information], which may increase the risk of toxicities. Avoid the use of BCRP inhibitors in patients treated with PIQRAY. If unable to use alternative drugs, when PIQRAY is used in combination with BCRP inhibitors, closely monitor for increased adverse reactions.

7.2 Effect of PIQRAY on Other Drugs
CYP2C9 Substrates
Coadministration of PIQRAY with CYP2C9 substrates (e.g., warfarin) may reduce plasma concentration of these drugs [see Clinical Pharmacology (12.3) in the full prescribing information]. Closely monitor when PIQRAY is used in combination with CYP2C9 substrates where decreases in the plasma concentration of CYP2C9 substrates may reduce activity of these drugs.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
PIQRAY is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for pregnancy information.

Based on animal data and mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes, including embryofetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures ≥ 0.8 times the exposure in humans based on AUC at the recommended dose of 300 mg/day (see Data). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

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

Data
Animal Data
In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of alpelisib up to 30 mg/kg/day during the period of organogenesis.

In rats, oral administration of alpelisib resulted in maternal toxicity (body weight loss, low food consumption) and no viable fetuses (post-implantation loss) at 30 mg/kg/day (approximately 3 times the exposure in humans at the recommended dose of 300 mg/day based on AUC). At a dose of 10 mg/kg/day (approximately 0.8 times the exposure in humans at the recommended dose of 300 mg/day based on AUC), toxicities included reduced fetal weight and increased incidences of skeletal malformations (bent scapula and thinned or bent long bones) and fetal variations (enlarged brain ventricle). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. However, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies in the U.S. general population.

In a pilot embryo-fetal development study in rabbits, a dose of 30 mg/kg/day resulted in no viable fetuses (post-implantation loss). Doses ≥ 15 mg/kg/day resulted in increased embryo-fetal deaths, reduced fetal weights, and malformations, mostly related to the tail and head. At 15 mg/kg/day in rabbits, the maternal exposure was approximately 5 times the exposure achieved at the recommended human dose of 300 mg/day based on AUC.

8.2 Lactation
PIQRAY is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for lactation information.

There is no data on the presence of alpelisib in human milk, its effects on milk production, or the breastfed child. Because of the potential for serious adverse reactions in the breastfed child, advise lactating women to not breastfeed during treatment with PIQRAY and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential
PIQRAY is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for contraception and infertility information.

Pregnancy Testing
Verify the pregnancy status in females of reproductive potential prior to initiating PIQRAY.

Contraception
Females
PIQRAY can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose.

Males
Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose.

Infertility
Based on findings from animal studies, PIQRAY may impair fertility in males and females of reproductive potential [see Nonclinical Toxicology (13.1) in the full prescribing information].

8.4 Pediatric Use
The safety and efficacy of PIQRAY in pediatric patients have not been established.

8.5 Geriatric Use
Of 284 patients who received PIQRAY in the SOLAR-1 trial, 117 patients were ≥ 65 years of age and 34 patients were ≥ 75 years of age. In patients treated with PIQRAY plus fulvestrant, there was a higher incidence of Grade 3-4 hyperglycemia in patients ≥ 65 years of age (44%) compared to patients < 65 years of age (32%). No overall differences in effectiveness of PIQRAY were observed between patients ≥ 65 years of age compared to younger patients. There are an insufficient number of patients ≥ 75 years of age to assess whether there are differences in safety or effectiveness.

8.6 Renal Impairment
The effect of severe renal impairment (Clcr < 30 mL/min) on alpelisib pharmacokinetics is unknown [see Clinical Pharmacology (12.3) in the full prescribing information].

No dose adjustment is recommended for patients with mild to moderate renal impairment (Clcr 30 to < 90 mL/min).

10 OVERDOSAGE
There is limited experience of overdose with PIQRAY in clinical trials. In the clinical studies, PIQRAY was administered at doses up to 450 mg once daily.

In cases where accidental overdose of PIQRAY was reported in the clinical studies, the adverse reactions associated with the overdose were consistent with the known safety profile of PIQRAY and included hyperglycemia, nausea, asthenia, and rash.

Initiate general symptomatic and supportive measures in all cases of overdose where necessary. There is no known antidote for PIQRAY.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
© Novartis
T2002-127A
Brigatinib Maintains Long-Term Efficacy in Crizotinib-Refractory ALK+ NSCLC

by CAROLINE SEYMOUR

In the phase 1/2 trial, patients with advanced malignancies (N = 137) received brigatinib at one of the following doses: 60 mg daily, 90 mg once daily, 120 mg daily, 90 mg followed by 180 mg once daily, 180 mg daily, or 240 mg daily or 300 mg once daily.

In the phase 2 trial, patients with locally advanced or metastatic ALK-positive NSCLC with disease progression on crizotinib who had not received any other ALK-directed therapy were randomized 1:1 to 90 mg of brigatinib once daily (arm A; n = 112) or 90 mg once daily for a 7-day lead-in followed by 180 mg once daily (arm B; n = 110).

Brain metastases at baseline were reported in 63%, 71%, and 67% of patients in the phase 1/2 trial and arm A and arm B of the phase 2 ALTA trial, respectively.

Additional findings from the phase 2 trial indicated that the intracranial ORR by independent review was 67% (95% CI, 41%-87%) among 18 patients with measurable central nervous system lesions, with a median intracranial DOR of 16.6 months (95% CI, 3.7-NR). Notably, the approved dosing regimen administered in arm B of the phase 2 trial was associated with a numerically higher ORR, PFS, and OS compared with the 90-mg daily dose that was administered in arm A of the trial.

The median intracranial PFS by independent review in 74 patients with any baseline brain metastases was 18.4 months (95% CI, 12.6-23.9), with an estimated 4-year intracranial PFS rate of 8% (95% CI, 2%-23%). Moreover, the safety profile of brigatinib was consistent with prior reports, with no new safety concerns.

On May 22, 2020, the FDA approved brigatinib for the frontline treatment of patients with ALK-positive metastatic NSCLC, as detected by an FDA-approved test.

For a full list of references, see the article at bit.ly/3izE3q0.
MOBOCERTINIB, A FIRST-IN-CLASS, ORAL, irreversible EGFR tyrosine kinase inhibitor (TKI), induced rapid, deep, and durable responses and a manageable safety profile in patients with platinum-pretreated EGFR exon 20 insertion–positive locally advanced or metastatic non–small cell lung cancer (NSCLC). This population, which represents approximately 10% of patients with EGFR-mutated NSCLC, typically progresses within 6 months of treatment with platinum-based chemotherapy and has limited response to available EGFR TKIs such as afatinib (Gilotrif), erlotinib (Tarceva), or gefitinib (Iressa).

Investigators of an ongoing phase 1/2 study (NCT02716116) examined mobocertinib as an option for overcoming EGFR resistance. “Mobocertinib is an orally administered TKI that is specifically being developed for the treatment of patients with EGFR [exon] 20 insertion mutations,” said Suresh S. Ramalingam, MD, FACP, executive director of the Lung Cancer Program of the Winship Cancer Institute of Emory University in Atlanta, Georgia and associate vice president for cancer of the Woodruff Health Sciences Center. “Among EGFR mutations, the insertion 20 mutations account for approximately 10%.”

Updated data from the phase 1/2 study were presented by Ramalingam during the 2021 American Society of Clinical Oncology Annual Meeting (TABLE). In the platinum-pretreated patient cohort (n = 114), the confirmed overall response rate (ORR) by independent review committee (IRC) assessment was 28% (95% CI, 20%-37%); all responses were partial responses (PRs). By investigator assessment, the confirmed ORR was 35% (95% CI, 26%-45%); the complete response (CR) rate was less than 1%, and the PR rate was 34%.

The median duration of response (DOR) was 17.5 months (95% CI, 7.4-20.3) by IRC and 11.2 months (95% CI, 5.6—not evaluable [NE]) by investigator assessment. The confirmed disease control rate (DCR) was 78% (95% CI, 69%-85%) by IRC and investigator assessment. The median overall survival was 24.0 months (95% CI, 14.6-28.8), and the median progression-free survival was 7.3 months (95% CI, 5.5-9.2).

“Based on these data, we believe that mobocertinib is a potential treatment option for patients with EGFR exon 20 insertion mutations,” said Ramalingam, who is also a professor in the Department of Hematology and Medical Oncology, the Roberto C. Goizueta Distinguished Chair for Cancer Research, assistant dean for Cancer Research, and director of the Division of Medical Oncology in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

Part 1 of the 3-part study utilized a 3 + 3 dose-escalation, phase 1 design to evaluate mobocertinib in patients with advanced NSCLC. Part 2 of the study utilized a phase 2 dose-expansion schema to evaluate daily mobocertinib at 160 mg.

In total, 7 cohorts and 1 extension cohort (EXCLAIM; part 3 of the study) will be evaluated. The median follow-up time was 14.2 months (range, 0.7-35.8) in the platinum-pretreated patient cohort and 13.0 months (range, 0.7-18.8) in the EXCLAIM cohort.

Cohort 1 evaluated patients who received prior platinum-based therapy and had refractory EGFR exon 20 insertion–positive mNSCLC and no active or measurable central nervous system metastases. Patients were a median age of 60 years (range, 27-84); 66% of patients were female, and the majority of patients were Asian (60%). Nearly all patients had adenocarcinoma histology (98%) and an ECOG performance status of 1 (75%). Notably, the majority of patients were never smokers (71%).

The median number of prior anticancer regimens was 2; 100% of patients received prior platinum-based chemotherapy, 43% received prior immunotherapy, and 25% received prior EGFR TKIs. Finally, 35% of patients had baseline brain metastases.

Additionally, findings from the EXCLAIM cohort of patients (n = 96) were presented in the virtual poster. Patients included

**MOBOCERTINIB Elicits Anticancer Activity in Platinum-Pretreated EGFR Exon 20 Insertion-Positive NSCLC**

by JESSICA HERGERT

**TABLE.** Efficacy Outcomes in Patients With Previously Treated EGFR Exon 20 NSCLC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PPP cohort (n = 114)</th>
<th>EXCLAIM cohort (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent review committee assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>28% (20%-37%)</td>
<td>25% (17%-35%)</td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>17.5 (7.4-20.3)</td>
<td>NE (5.6-NE)</td>
</tr>
<tr>
<td>Confirmed DCR (95% CI)</td>
<td>78% (69%-85%)</td>
<td>76% (66%-84%)</td>
</tr>
<tr>
<td><strong>Investigator assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>35% (26%-45%)</td>
<td>32% (23%-43%)</td>
</tr>
<tr>
<td>CR</td>
<td>&lt; 1%</td>
<td>1%</td>
</tr>
<tr>
<td>PR</td>
<td>34%</td>
<td>31%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>11.2 (5.6-NE)</td>
<td>11.2 (7.0-NE)</td>
</tr>
<tr>
<td>Confirmed DCR (95% CI)</td>
<td>78% (69%-85%)</td>
<td>75% (65%-83%)</td>
</tr>
</tbody>
</table>

CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; NSCLC, non–small cell lung cancer; ORR, overall response rate; PPP, platinum-pretreated population; PR, partial response.
in the EXCLAIM cohort had previously treated EGFR exon 20 insertion-positive mNSCLC. In this cohort, 86 patients had received prior platinum-based therapy.

Baseline patient characteristics were similar in this cohort vs the platinum-pretreated patient cohort. The median patient age was 59 years (range, 27-80), 65% of patients were female, and most patients were of Asian descent (69%). The majority of patients had adenocarcinoma histology (99%) and an ECOG performance status of 1 (71%). Most patients were never smokers (73%).

The median number of prior lines of anti-cancer therapy in the EXCLAIM cohort was 1; 90% of patients received prior platinum-based chemotherapy, 34% received prior immunotherapy, and 31% received prior EGFR TKIs. Finally, 34% of patients had baseline brain metastases.

In this cohort, the confirmed ORR by IRC was 25% (95% CI, 17%-35%); all responses were PRs. The confirmed ORR by investigator assessment was 32%; 1% of patients achieved a CR and 31% achieved PRs.

The median DOR was NE (95% CI, 5.6-NE) by IRC and 11.2 months (95% CI, 7.0-NE) by investigator assessment. The confirmed DCRs were 76% (95% CI, 66%-84%) and 75% (95% CI, 65%-83%), respectively.

In the EXCLAIM cohort, 60% (n = 58) of patients experienced progressive disease by investigator assessment. The brain was the first site of progressive disease in 38% (n = 22) of these patients. Of these patients, 23% (n = 5) continued on mobocertinib for at least 3 months after initial progressive disease. The median time on treatment beyond initial progressive disease was 1.6 months (95% CI, 0.2 to 6.7).

Additionally, in the remaining 62% of patients (n = 36) who experienced progressive disease in initial sites other than the brain, 6% (n = 2) continued on mobocertinib for at least 3 months after initial progressive disease. The median time on treatment beyond initial progressive disease was 0.1 months (95% CI, 0.0 to 10.0).

In the EXCLAIM cohort, 33 patients had brain metastases at baseline. Of these patients, 76% (n = 25) developed progressive disease by investigator assessment, 68% of which reported the brain as the first site of progressive disease.

Additional results indicated that 23% of patients (n = 26) in the platinum-pretreated patient cohort and 26% of patients (n = 25) in the EXCLAIM cohort remained on mobocertinib at the time of the data cutoff. The median time on treatment was 7.4 months (range, 0.0-34.0) and 6.8 months (range, 0.0-18.8), respectively.

"Nearly 85% of patients in this study had some level of tumor shrinkage [with mobocertinib]…and nearly 50% of patients with an objective response still have an ongoing response at the time of data cutoff for this presentation," Ramalingam said.

Notably, in the platinum-pretreated patient cohort, responses were observed in all evaluated subgroups irrespective of prior EGFR TKI treatment, prior immunotherapy, or EGFR exon 20 insertion mutation variant. Additionally, the safety profile observed with mobocertinib was consistent with the known profiles of EGFR TKIs.

Regarding safety in the platinum-pretreated patient cohort, all patients (100%) reported any-grade adverse effects (AEs), and 99% of patients reported any-grade treatment-related AEs (TRAEs). Of these, any grade 3 or greater AEs were observed in 69% of patients and any grade 3 or greater TRAEs were observed in 47% of patients.

Serious AEs were noted in 49% of patients; 46% of these were grade 3 or greater. A quarter of patients (25%) experienced an AE that led to dose reduction and 17% experienced an AE that led to treatment discontinuation.

In the EXCLAIM cohort, any type of any-grade AEs were reported in 100% of patients, 66% of which were grade 3 or greater. Nearly all patients (99%) reported any-grade TRAEs, 42% of which were grade 3 or greater. Serious AEs were observed in 47% of patients, of which 44% were grade 3 or greater. Additionally, 22% of patients experienced an AE that required dose reduction, and 10% of patients experienced an AE that required treatment discontinuation.

Nausea and diarrhea were the most frequently reported AEs that required treatment discontinuation in the EXCLAIM cohort. Other AEs included rash, paronychia, decreased appetite, dry skin, increased creatinine level, stomatitis, vomiting, dermatitis aciform, pruritus, and increased amylase level. Of note, 1 treatment-related death from cardiac failure occurred in the EXCLAIM cohort in a platinum-pretreated patient.

In the EXCLAIM cohort, patient-reported outcome data demonstrated mean improvements from baseline in European Organisation for Research and Treatment of Cancer (EORTC) QLQ-LC13 scores for dyspnea, cough, and pain in chest. Despite worsening gastrointestinal symptom scores, mean EORTC QLQ-C30 Global Health Status/Quality of Life scores were preserved with mobocertinib.

**REFERENCE**

INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:

- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-medullary thyroid cancer [non-MTC]), and advanced or metastatic RET-mutant MTC

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 17.5 months</strong></td>
</tr>
<tr>
<td>(95% CI: 12, NE)</td>
<td>(95% CI: 12, NE)</td>
</tr>
<tr>
<td>median follow-up: 7.4 months&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>median follow-up: 12.1 months&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Responses in intracranial lesions were observed in 10 of 11 pre-treated patients with measurable brain metastases**<sup>1,3</sup>

**CNS DoR was ≥6 months in all responders with measurable brain metastases**<sup>1,3</sup>

**No patients received radiation therapy to the brain within 2 months prior to study entry**<sup>1,3</sup>

Find RET. Find results on Retevmo.com.

**Adverse Reactions and Laboratory Abnormalities**

- The most common adverse reactions, including laboratory abnormalities, (>25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction (in >2% of patients) was pneumonia. Fatality adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 3% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.

<sup>1</sup>Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.<sup>2</sup>

<sup>2</sup>Patients previously treated with platinum-based chemotherapy and with measurable CNS lesions at baseline according to IRC assessment.<sup>3</sup>

<sup>3</sup>Patients in this cohort received prior systemic therapy (including sorafenib, lenvatinib, or both) other than RA1.<sup>4</sup>

<sup>4</sup>The efficacy of Retevmo was evaluated in 55 patients with RET-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.<sup>5</sup>

<sup>5</sup>Number of patients included in the initial efficacy analysis. Efficacy was based on patients who had at least 6 months of follow-up.<sup>6</sup>

<sup>6</sup>Efficacy was evaluated in 105 adult patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. At 105 patients received systemic therapy, 59 of the 105 patients received a prior multitargeted inhibitor (MTI).<sup>7</sup>

<sup>7</sup>Patients with RET-mutant NSCLC and RET-mutant thyroid cancer (non-MTC) were not enrolled in the trial since RET is not the driver of tumor growth in these cancers.<sup>8</sup>

<sup>8</sup>BID=twice daily; CI=confidence interval; CNS=central nervous system; CR=complete response; Diff=duration of response; NE=not estimable; ORR=objective response rate; PO=orally; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Retevmo<sup>®</sup> is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates.

PP-SE-US-0397 11/2020 © Lilly USA, LLC 2020. All rights reserved.
Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhoea. Correct hypokalaemia, hypomagnesaemia and hypocalcaemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity of the event.

Serious, including fatal, haemorrhagic events can occur with Retevmo. Grade ≥3 haemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3.0% patients with fatal haemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3–4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were hypertension (18%), prolonged QT interval (4%), diarrhoea (3.4%), dyspepsia (2.3%), fatigue (2%), abdominal pain (1.9%), haemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥2% of patients) was pneumonia.

**Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.**

**References:**
RETEVMO™ (selpercatinib) capsules, for oral use
Initial U.S. Approval: 2020

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE
RETEVMO (selpercatinib) is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion-positive thyroid cancer who require systemic therapy are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS:
None

WARNINGS AND PRECAUTIONS

Hypertotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 8%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.4% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity.

QT Interval Prolongation
RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia/tachyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diabetes, Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

RETEVMO™ (selpercatinib) capsules, for oral use

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on data from animal reproduction studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposure that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryopathy and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final dose.

ADVERSE REACTIONS

Clinical Trial 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.

RETEVMO for Gene Fusion or Gene Mutation Positive Solid Tumors
The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001. Among 702 patients who received RETEVMO, 65% were exposed for 6 months or longer and 34% were exposed for greater than one year. Among these patients, 95% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (47%), MTC (44%), and non-medullary thyroid carcinoma (5%).

Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most frequent serious adverse reaction in > 2% of patients was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in < 1 patient included sepsis (n = 3), cardiac arrest (n = 3) and respiratory failure (n = 3).

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

Dose interruptions due to an adverse reaction occurred in 42% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

Dose reductions due to an adverse reaction occurred in 31% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included ALT increased, AST increased, QT prolongation and fatigue.

The most common adverse reactions, including laboratory abnormalities, (≥ 25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

Table 1 summarizes the adverse reactions in LIBRETTO-001.

<table>
<thead>
<tr>
<th>Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Dry Mouth</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

RETEVMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08/MAY/2020

RETEVMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08/MAY/2020
Table 2: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (N=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
</tr>
<tr>
<td>Diaphorescence</td>
<td>16</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

Clinically relevant adverse reactions in ≥15% of patients who received RETEVMO include hypothyroidism (9%).

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 2: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
</tr>
</tbody>
</table>

Increased Creatinine
In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS
Effects of Other Drugs on RETEVMO
Acid-Reducing Agents
Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally acting antacid).

Strong and Moderate CYP3A Inhibitors
Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A Inducers
Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations, which may reduce RETEVOM anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

Effects of RETEVMO on Other Drugs
CYP2C8 and CYP3A Substrates
RETEVMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval
RETEVMO is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposure levels that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

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

Data
Animal Data
Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

Lactation
Risk Summary
There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the final dose.
Clinically relevant adverse reactions in <15% of patients who received RETEVMO include:

- Cough, productive cough
- Diarrhea, defecation urgency, frequent bowel movements
- Abdominal pain
- Hemorrhage
- Rash
- Dyspnea
- Hemorrhage
- Skin reactions
- Edema

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased glucose</td>
<td>22</td>
<td>0.7</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
<td>0.7</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
</tr>
</tbody>
</table>

Hematology

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Nervous System

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>5</td>
<td>27</td>
</tr>
</tbody>
</table>

Skin

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

Animal Data

In 4-week general toxicity studies in rats, animals showed signs of physseal hypertrophy and tooth dysplasia at doses resulting in exposures ≥ approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physseal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (≥1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Geriatric Use

Of 792 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were > 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] ≥30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr <30 mL/min) or end-stage renal disease.

Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

Ro only.

Additional information can be found at www.retevmo.com.

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA
Copyright ©2020, Eli Lilly and Company. All rights reserved.

SE HCP BS 08MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use  

SE HCP BS 08MAY2020
THE USE OF ONCOLOGY BIOSIMILARS
has expanded rapidly in the United States
during the past 2 years as providers
embraced a growing armamentarium of new
products, according to findings from real-
world data reported at the 2021 American
Society of Clinical Oncology Annual
Meeting (ASCO 2021). Results of several
analyses also show that biosimilars are
starting to make an impact on the cost of
providing care.

Overall, 11 biosimilars have been
launched in the oncology market since
January 2019, bringing the total number of
FDA-approved biosimilars for cancer care
to 14. Investigators who sought to measure
oncologists’ response to the new crop of
agents reported initial hesitation, followed
by robust uptake and hefty savings. They
noted that the biosimilar competition had
little effect on reference product prices,
which "remained stable."1

The findings were reported in an abstract
published at ASCO 2021. Investigators drew
their data from 2020 prescription infor-
mation published by Wolters Kluwer for
2020 (n = 130,836), sales data from IQVIA,
and dosage information published by ION
Solutions (n = 69,884). The analysis included
information for patients taking bevacizumab
(Avastin), trastuzumab (Herceptin), or
rituximab (Rituxan) or an FDA-approved
biosimilar for these drugs.

Investigators found that in 2020, 8.2%
aturally new prescriptions for bevacizumab,
rituximab, and trastuzumab were for biosim-
ilar versions. For bevacizumab, there are
currently 2 biosimilars available; for ritux-
imab, there are 3, and for trastuzumab, 5.

Findings for use of trastuzumab biosimi-
lars revealed a dramatic increase from the
first year of availability to the next. In the
first 3 months of 2019, 7.3% of patients initi-
ating first-line treatment were prescribed
the trastuzumab biosimilar vs the reference
product. In the first quarter of 2020, when
all 5 trastuzumab biosimilars had become
available, the new prescriptions rate was
80.5% for patients receiving first-line care.

Uptake rates differed for individual
biosimilars. The investigators reported
that rituximab-pvvr (Ruxience), which
was approved in July 2019, had an initial
uptake of just 2.3%. At the same time, they
did observe willingness among oncologists
to switch patients from reference products
to biosimilars as time went on. They noted
that 11.1% of patients (bevacizumab, 11.3%;
trastuzumab, 14.1%; rituximab, 7.9%) were
transitioned from the reference biologics to
biosimilars during treatment.

“Uptake was particularly rapid for tras-
tuzumab biosimilars,” investigators said.

Among patients on trastuzumab at the time
of its first biosimilar launch, 18.2% switched
to trastuzumab-anss [Kanjinti] in the first
90 days postlaunch.”

Significant savings were a feature of the
use of biosimilars in the oncology practices,
the authors said. Costs per biosimilar
prescription were lower than those of the
reference product by 42.0%, 29.9%, and 89.5%
for trastuzumab, rituximab, and bevac-
izumab, respectively.

“However, biosimilar launches had
little impact on reference product pricing,
with 2019 to 2020 year-over-year differ-
ces in price per prescription close to the
year-over-year averages in previous years
(2015-2019) for all 3 reference products,”
the authors wrote.

AUTOMATIC SUBSTITUTION
YIELDS SAVINGS

At Texas Oncology, a network with more
than 250 locations throughout Texas and
southeastern Oklahoma, the care team
sought to increase the use of biosimilars in
community practices by streamlining the
process of substituting biosimilars for the
reference products.

A program that enabled automatic
prescribing of biosimilars resulted in
dramatic savings and increased usage rates
for biosimilar vs originator products, inves-
tigators reported at ASCO 2021.2 Although
biosimilars offer the potential for thera-
apeutically equivalent outcomes to branded
drugs at a lower cost, they can be difficult
to prescribe, Lalan S. Wilfong, MD, said
in presenting the findings. Wilfong is vice
president of quality programs and value-
based care at Texas Oncology.
“Therapeutic interchange is complicated by the awkward designation of biosimilars, which limits simple substitution,” Wilfong said. “Generic drugs can be substituted by a pharmacist without any approval at all because they’re designated generics. However, the way biosimilars are designated requires that a physician approve a therapeutic interchange of a drug because it is not considered generic substitution. It is a biosimilar. So it requires a physician approval as well as patient consent for the therapy interchange of biosimilars to occur.”

In the Texas Oncology program, a central pharmacy team reviewed all prescriptions and substituted biosimilars for originator biologics unless payers insisted otherwise or the relevant biosimilar was not in the practice formulary. Texas Oncology also compiled a weekly report identifying all patients who would benefit from switching to biosimilars, and substitutions were then made. In collaboration with McKesson Specialty Health, patient and clinician education was incorporated into the biosimilar usage effort to improve results.

Texas Oncology began the substitution in July 2020 with rituximab and followed up in September 2020 and October 2020 with bevacizumab and trastuzumab substitutions, respectively. By December 2020, utilization of biosimilars rose to 77% from 5% for rituximab, to 88% from 9% for bevacizumab, and to 74% from 8% for trastuzumab.

Investigators calculated the potential savings per administration at $550 for bevacizumab, $850 for trastuzumab, and $1400 for rituximab.

“In 1 month alone, this project dramatically reduced cost by $4 million or 21% by conversion to these 3 biosimilars,” they wrote.

The investigators also predicted that additional savings would be possible by using multidose vials of biosimilar product rather than single-dose vials.

“Biosimilar conversion can be rapidly accomplished via physician-approved, pharmacist-driven care-team approach,” Wilfong said. “And it does require the entire care team to be involved because of the difficulty in simply just converting patients to biosimilars—the drugs have to be substituted, physician approved, and patient reconsented.”

MODEL FORECASTS SAVINGS

To assess the potential cost savings that could be realized through the use of biosimilars, academic and industry investigators developed a model designed to measure the impact on the US health care system of substituting rituximab-abbs (Truxima) for the combination of rituximab/hyaluronidase human (Rituxan Hycela). Rituximab-abbs, which is administered intravenously, became the first FDA-approved rituximab biosimilar in November 2018. The FDA approved subcutaneous rituximab/hyaluronidase (SC-R) in June 2017.

The model demonstrated incremental annual savings of $2359 to $8186 per patient with non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) with the biosimilar, according to data reported at ASCO 2021.3

Investigators based their savings analysis on a 5-million-member insured population (Medicare), in which 972 patients would be treated for NHL or CLL during a 1-year span. Of those patients, 49 would receive SC-R. For the study, investigators assumed that 25% of the 49 patients (n = 13) would receive intravenous biosimilar treatment (IV-R-BIOSIM).

The 1-year model factored in drug and administration costs and assumed efficacy and safety would be equivalent between the 2 cohorts. For the IV-R-BIOSIM dosing, the investigators assumed body surface area of 1.8 m². They also assumed annual dose counts with either IV-R-BIOSIM or SC-R of 10 for patients with untreated follicular lymphoma (FL) with maintenance therapy; 8 for untreated FL without maintenance, relapsed/refractory FL, or untreated diffuse large B-cell lymphoma (DLBCL); and 6 for CLL. Duration of IV-R-BIOSIM infusion was assumed to be 3 hours. SC-R costs included an initial intravenous rituximab dose. For the 13 patients who received the hypothetical IV-R-BIOSIM dosing, estimated total 1-year savings were $57,864. The investigators said their budget impact model was most sensitive to low or high body surface area dosing and the proportion of patients with CLL. On a per-patient basis, the annual incremental savings with IV-R-BIOSIM was projected at $8186 for untreated FL with maintenance, $6654 for untreated FL without maintenance, relapsed/refractory FL, or untreated DLBCL; $2359 for CLL; and $5126 for NHL with 2-year maintenance.

“These findings demonstrate the potential economic benefits of IV-R-BIOSIM vs SC-R that may result in expanded access to rituximab therapy,” investigators said.

REFERENCES


In 2020, biosimilars accounted for 8.2% of new prescriptions for bevacizumab, rituximab, and trastuzumab.
Comprehensive Treatment Approach Advances Care for Patients With Early-Stage Breast Cancer

by GWENDOLYN M. BRYANT-SMITH, MD; CHRISTOPHER JEAN-LOUIS, DO, MPH; AND RONDA S. HENRY-TILLMAN, MD

PARADIGM SHIFTS IN BREAST CANCER treatment necessitate a team approach. Comprehensive treatment provided by a specialized group of experts has become the standard of care in breast cancer. A one-size-fits-all treatment approach no longer works for these patients—it takes a multidisciplinary team and a personalized patient approach to achieve the best outcomes. Advances in the diagnosis and treatment of early-stage breast cancer (ESBC) highlight the need for clinicians to adapt to paradigm shifts that will have notable effects on patient care.

Breast cancers are typically defined by stage and biological behavior. These descriptors aid the multidisciplinary breast team in making care decisions. The primary objective of breast cancer treatment is early detection, which allows for removal of the cancer without metastasis or recurrence.

With advancements and improved knowledge of the biological behavior of breast cancer, the American Joint Committee on Cancer Staging Manual, 8th edition, incorporated additional biological prognostic factors that facilitate predictions of disease severity. These factors include anatomic, clinical, and pathologic biomarkers. 1

Size, spread, grading, biomarkers (estrogen receptor, progesterone receptor, HER2), Ki-67, and recurrence score are also evaluated. Understanding stage and biological behavior allows for a better prediction of outcomes and decisions related to treatment.

Stage 0 disease includes ductal carcinoma in situ (DCIS). In situ early cancers are contained within the basement membrane of the duct or lobule. Stage I and IIA define early invasive breast cancers that have penetrated or grown through the basement membrane with low or intermediate grade proliferation rates without spread to regional nodes.

ESBC is a cancer that has not grown outside of the breast and has a low-grade biological profile of stage 0 to IIA. Numerous advances in diagnostic, surgical, and oncologic management of ESBCs have been made. Data from phase 1 prospective basic, translational, and clinical trials to single institutional studies have been published validating impact and advances. Consensus statements and clinical practice guidelines have enhanced the care of patients providing guidelines for prevention through survivorship. 2

Screening and diagnostic detection have advanced through the incorporation of digital breast tomosynthesis (DBT), breast ultrasound, and breast MRI. Protein-targeted therapies, including biological response modifiers and hormone-targeted endocrine therapy, continue to be major components of treatment. As the treatment paradigm of breast cancer continues to shift, less aggressive techniques (de-escalation) with targeted therapies may prove comparable to conventional surgery, chemotherapy, and radiation.

ADVANCES IN SCREENING AND DIAGNOSIS: BREAST IMAGING

DBT, also known as a 3-dimensional mammogram, is increasingly becoming the first-line standard in mammography breast cancer screening. DBT was approved by the FDA in 2011. Studies consistently have shown that using DBT leads to increased invasive breast cancer detection and decreased call backs and additional work-ups for noncancer. Even with these improvements in mammography, breast density continues to be a limiting factor in breast cancer detection, necessitating the need for other supplemental screening tools such as screening breast ultrasound and screening breast MRI.

Breast ultrasound is both a diagnostic and a screening tool. In the diagnostic setting, it is used to further evaluate masses, asymmetries, and architectural distortion noted on mammography. It is also used as a first-line diagnostic tool in female patients younger than 30 years who present with a palpable lump. Ultrasound is helpful in distinguishing between a benign cyst and a suspicious mass.

Notably, breast ultrasound has become very useful in the screening setting in low- and middle-resource countries. 3,4 Breast ultrasound is also important as a complementary screening tool to mammography in patients with an elevated lifetime risk of breast cancer who are unable to undergo breast MRI. Additionally, it can be a supplement screening tool for patients with intermediate-risk disease who have dense breast tissue.

Breast ultrasound as a complement to mammography in these patients finds approximately 2 to 4 more cancers per 1000 patients compared with screening mammography alone. 5 Digital breast mammography
without tomosynthesis typically finds 4.4 to 4.6 cancers per 1000 patients; DBT finds 5.4 cancers per 1000 patients.\textsuperscript{6,7} Adding breast ultrasound screening to mammography screening has been shown to find 2 to 4 more primarily node-negative invasive breast cancers per 1000 patients.\textsuperscript{6,7} However, this increase in cancer detection with screening ultrasound is a trade-off to finding and possibly performing a biopsy for benign disease.

Breast MRI is a complementary imaging study to mammography and is used in both the diagnostic and screening settings for breast cancer detection. MRI not only evaluates the morphology of masses but also the physiology of masses, nonmass enhancement, and foci through gadolinium contrast enhancement.

As a diagnostic tool, it is used to evaluate the extent of disease in patients with newly diagnosed breast cancers and patients’ response to neoadjuvant chemotherapy. In the screening setting, it evaluates high risk patients with a greater than 20% lifetime risk of breast cancer by a mathematical risk assessment model, patients with genetic mutations that predispose them to breast cancer, and patients who have undergone chest irradiation between the ages of 10 to 30 years. Screening breast MRI detects an additional 14 cancers per 1000 patients screened, which is in addition to those noted on mammography.

**TREATMENT CONSIDERATIONS**

The 2 mainstay surgical options for the treatment of ESBC are lumpectomy and mastectomy with or without axillary evaluation. One major advance is the utilization of oncoplastic surgical techniques, which have contributed to improved surgical outcomes. Several additional advanced techniques have been implemented for the correction of associated breast defects and reshaping the natural breast contour. These techniques include lumpectomy with tissue rearrangement and therapeutic breast reduction for symmetry.

The round block/Benelli technique for skin reduction provides an approach for cancers located in distant quadrants of the breast. The hidden scar approach is a technique that allows the surgical site to be hidden and yields a superior cosmetic outcome with either lumpectomy or mastectomy.\textsuperscript{8} In patients receiving mastectomies, the angel wing technique for lateral adiposity allows for flat mastectomies with removal of redundant medial and lateral adipose tissue.\textsuperscript{9}

Some patients with ESBC and a favorable biology may be candidates for deescalation. Over the past 10 years, there has been a major paradigm shift in the management of the axilla in ESBCs, including axillary lymph nodal dissection (ALND) and the elimination of nodal evaluation in patients receiving lumpectomy with a diagnosis of DCIS (stage 0).

In early-stage invasive breast cancer, the ACOSOG Z0011 trial (NCT00003855) demonstrated that omitting ALND with 1 to 2 positive sentinel lymph nodes in patients receiving breast conservation lumpectomy and radiation was not inferior to...

---

**PATIENT CASE PRESENTATION**

A 38-year old woman presents with a palpable right breast lump.

Digital Breast Tomosynthesis Synthetic Mammographic Views

Triangle denotes a palpable lump in the right breast and an adjacent 3.1-cm oval, equal-density mass with indistinct margins in the right breast at approximately 8 o’clock to 9 o’clock at posterior depth which is marked by an arrow.

Breast Ultrasound

Dilated ducts are seen on ultrasound at the site of the right breast palpable lump.

Breast MRI

Blue arrows show extensive segmental, heterogenous, nonmass enhancement in the right breast, larger than what was anticipated by mammography and ultrasound. Extensive DCIS was observed.

Blue arrow in the left breast shows linear, clumped, nonmass enhancement that was biopsied and proven to represent DCIS in the contralateral breast. Finding was not noted on mammography.

Palpable lump biopsied under ultrasound reveal ductal carcinoma in situ (DCIS) nuclear grade 2.
Survivorship

It is not surprising that mortality rates have steadily fallen in concert with advances in the breast cancer care platform. Currently, more than 90% of patients with ESBC have a projected survival of greater than 5 years. However, numerous considerations must be taken into account when assessing this population. These patients remain at risk indefinitely for local recurrence, systemic recurrence, and contralateral new primary breast cancers. In addition, breast cancer survivors also need multidisciplinary care to manage complications or secondary effects from their previous cancer treatments.

Optimizing care for this patient population is critical to the overall health care landscape and has led to greater focus on breast cancer survivorship care. Numerous studies have evaluated the benefit of early detection by circulation tumor biomarkers or advanced imaging on recurrence and survival outcomes. However, there is still no solid correlation. Current data and consensus recommendations from the American Society of Clinical Oncology and the American College of Physicians state that a performance of yearly screening mammography is the only tool supported by evidence from randomized clinical trials to affect mortality and survivorship. Other important items such as bone health, fertility/infertility, psychological health, and adherence to screening require a multispecialty team approach and follow-up. Therefore, in our survivorship program, we recommend yearly mammography for patients who have undergone breast conservation and additional tests or imaging based on patients’ symptoms.

We must embrace a multidisciplinary team approach and continue to develop personalized care plans for each of our patients with breast cancer.

REFERENCES

Nominate a dedicated and deserving nurse to be an Oncology Nurse Champion!

Do you know a nurse who goes above and beyond to make a measurable difference to improve patient outcomes through exceptional supportive care?

We are now accepting nominations from health care professionals, colleagues, patients, friends, and family of outstanding nurses who demonstrate these admirable qualities:

• Ability to help educate both patients and families about the cancer they face and their treatment path
• Knack for showing kindness, patience, and compassion in the face of difficulties faced by their patients
• Understanding of the science and how treatments are designed to overcome their patient’s cancer
• Aptitude to go above and beyond in Supportive Care for Patients and Patient Families

Scan the code to nominate a nurse to become an Oncology Nurse Champion!
Global Real-World Data Establish TheraSphere Y-90 as Optimal Choice for HCC

by BRITTANY LOVELY

**THERASPHERE Y-90 GLASS MICROSPHERES** offer a precision medicine technique aimed at delivering high-dose radiation directly to tumors. Most recently, investigators examined data from the retrospective TARGET study (NCT03295006), which aimed to provide a validated consensus between absorbed doses, adverse effects (AEs), and objective response rates (ORR) of the therapy in patients with hepatocellular carcinoma (HCC).

Specifically, the primary objective of the study was to use an alternative 2-compartment TheraSphere dosimetry methodology to calculate normal tissue-absorbed dose to then establish a relationship with grade 3 or higher hyperbilirubinemia without disease progression. Secondary measures included establishing a relationship between tumor-absorbed dose and objective response, overall survival (OS), and probability of α-fetoprotein (AFP) response.

Principal investigator Riad Salem, MD, walked through the latest data from the TARGET study as part of an OncLive® Rapid Readouts video program. Salem is vice chair for image guided therapy, chief of vascular and interventional radiology, and professor of radiology, medicine, and surgery at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois.

TheraSphere, a personalized selective internal radiation therapy for local tumor control in patients with HCC whose tumors measure 1 to 8 cm in diameter, was approved by the FDA in March based on results of the retrospective LEGACY study. At a median follow-up of 29.9 months, the therapy elicited an ORR of 72.2% (95% CI, 64.9%-78.5%) among 162 patients, the majority of whom (76.1%; 95% CI, 67.6%-82.9%) experienced a duration of response lasting at least 6 months.

**ESTABLISHING SYMMETRY WITH TARGET**

In TARGET, the treated population consisted of 209 patients with a median age of 66 years (range, 27-87). A majority of patients has Barcelona Clinic Liver Cancer C status (54.5%), Child-Pugh A status (89.5%), and unilobar disease (70.8%). The target lesion size ranged from 3 cm to at least 8 cm per RECIST 1.1 criteria. Forty-one patients (19.6%) had tumors measuring between 3 cm and less than 5 cm, 72 had tumors between 5 cm and less than 8 cm, and 96 patients had tumors at least 8 cm in diameter. Of note, 69.5% of patients had a total of 1 lesion, 21.5% had 2,
6.7% had 3, and 2.4% had between 4 and 10 target and nontarget lesions.

In an analysis of the correlation between grade 3 hyperbilirubinemia and normal tissue-absorbed dose, only 4.8% of patients experienced the AE. “When you look at the [data for the] first primary end point, we did not find a relationship,” Salem said. “Less than 5% of the patients experienced [the AE], so that [relationship] was actually not found, which is a good thing, because it shows that there’s room for optimization and even increasing of the dose when performing this kind of therapy.”

AEs of any grade were reported for 62.7% of the TARGET study population: 24.9% were grade 1, 17.2% were grade 2, 16.3% were grade 3, and 4.3% were grade 4. “If you look at all of the AEs that were identified, 63% of patients had AEs that [are] what you would expect in [patients with] HCC with some fatigue, pain, weakness, asthenia, and some very minor nausea,” Salem said. Specifically, all-grade AE rates were under 20% for fatigue (16.3%), abdominal pain (12.4%), asthenia (9.1%), and nausea (5.3%). Reported grade 4 AEs included ascites (0.5%), lymphocyte count decrease (1.4%), and decreased appetite (0.5%).

HIGH DOSE CORRELATES WITH RESPONSE

“As we hypothesized, the higher the delivered dose, the higher the response rate and, in particular, the complete response rate,” Salem noted on the response data. “You can stratify this patient population by absorbed dose. If you look at the entire patient population, 71% had an objective response, and interestingly, there was a significantly higher dose delivered to the tumor in responders compared with the nonresponders.”

Specifically, data from TARGET demonstrated an ORR of 70.8% (95% CI, 64.3%-76.6%) among all treated patients. The responders had a significantly higher tumor-absorbed dose (22.5.5 Gy; 95% CI, 201.0-253.0) compared with nonresponders (188.3 Gy; 95% CI, 164.6-215.3). In terms of complete responses, the rates increased from approximately 10% at a dose less than 225 Gy to over 30% with a dose of at least 300 Gy.

“The higher the dose, the more likely you are to achieve a response, which is something that you might expect and now that’s something that we are now demonstrating,” Salem said.

The OS data—“the gold standard in oncologic analyses,” Salem noted—also demonstrated a relationship with dosage. The median OS was 20.3 months (95% CI, 16.7-26.4) with an HR that corresponded to every 100 Gy change in tumor-absorbed dose of 0.826 (95% CI, 0.71-0.95; P = .009). Salem said that increase in tumor-absorbed dose is independently associated with increased OS.

Finally, the end point of the association between absorbed dose and the probability of AFP response 90 days post treatment was reported. In 71 patients with AFP level of at least 200 ng/mL at baseline, 38.0% had a response at 90 days posttreatment. In 107 patients who had an AFP of at least 20 ng/mL at baseline, 38.3% had a response in the same time frame. Investigators noted that the absorbed dose to total perfused tumor was significantly associated with AFP response at 90 days (P < .05).

“In some cases, AFP is a surrogate of OS, a surrogate of response…if you pick a strict AFP level of 200, nearly 40% of patients showed a response at day 90. So again, the absorbed dose was related to the AFP response,” Salem said.

FURTHER SUPPORT FOR PERSONALIZED DOSIMETRY

Investigators have demonstrated that personalized dosimetry is associated with significant response rates when compared with standard dosimetry and should be used for the development of trials using selective internal radiation approaches, particularly those with the Y-90 glass microspheres.

 “[The TARGET findings] are consistent with [results of] other clinical trials that have been published historically, in particular the DOSISPHERE-01 study that showed that patients survive longer when you perform individualized patient dosimetry,” Salem said.

Data from the phase 2 DOSISPHERE-01 trial (NCT02582034) showed that optimized treatment with TheraSphere was significantly more efficient than a standard dose. The study examined patients with unresectable locally advanced HCC across 4 health centers in France who had at least 1 measurable lesion measuring at least 7 cm in diameter. Patients were randomly assigned to either standard dosimetry (120 ± 20 Gy) or personalized dosimetry (≥205 Gy).

In total, 28 patients were assessed in each group as a modified intention-to-treat population. The ORR in the personalized therapy group was 71% (95% CI, 51%-87%) compared with 36% (95% CI, 19%-56%) in the standard therapy group (P = .0074).

REFERENCES


ONCLIVE ON AIR® FDA APPROVAL INSIGHTS

TUNE IN to hear more from Riad Salem, MD, on the unique elements of radioembolization technology, as well as learn more about the data that supported the regulatory approval of TheraSphere Y-90 glass microspheres for patients with hepatocellular carcinoma.
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively.

The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci 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: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

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

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. 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 pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS
The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions.

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

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

DRUG INTERACTIONS
CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS
Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib)

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. [See Use in Specific Populations].

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hemorrhage [see Warnings and Precautions]
- Infections [see Warnings and Precautions]
- Cytopenias [see Warnings and Precautions]
- Cardiac Arrhythmias and Cardiac Failure [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.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to IMBRUVICA in 6 trials as a single agent at ≥ 420 mg orally once daily in 475 patients and at ≥ 560 mg orally once daily in 174 patients and in 4 trials administered in combination with other drugs at ≥ 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies, 87% were exposed for ≥ 6 months and 68% were exposed for greater than one year. In this pooled safety population of 1,476 patients with B-cell malignancies, the most common adverse reactions (≥ 30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure to IMBRUVICA in one single-arm, open-label clinical trial (Study 1102) and five randomized controlled clinical trials (RESONATE, RESONATE-2, HELIOS, ILLUMINATE, and E1912) in patients with treatment-naive CLL/SLL (n=2,016 total, including n=1,133 patients exposed to IMBRUVICA) in general, patients with creatinine clearance (Clcr) ≥ 30 mL/min, ALT or AST ≥ 2.5 x ULN, or total bilirubin ≥ 1.5x ULN (unless of non-hepatic origin) were excluded from these trials. In Study E1202, patients with AST or ALT > 3 x ULN prior to starting treatment with IMBRUVICA had a median time from initiation of IMBRUVICA to ≥ 2.5 x ULN of 174 days and in 4 trials that allowed treatment with other drugs at ≥ 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies who received IMBRUVICA, 87% were exposed for ≥ 6 months and 68% were exposed for greater than one year. In this pooled safety population of 1,476 patients with B-cell malignancies, the most common adverse reactions (≥ 30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

CHRISTIAN ARRHYTHMIAS AND CARDIAC FAILURE: FATAL AND SERIOUS CARDIAC ARRHYTHMIAS AND CARDIAC FAILURE HAVE OCCURRED WITH IMBRUVICA. GRADE 2, 3, OR 4 ARRHYTHMIAS OCCURRED IN 6% OF PATIENTS AND GRADE 3 OR 4 CARDIAC FAILURE OCCURRED IN 1% OF 1,476 PATIENTS WHO RECEIVED IMBRUVICA IN CLINICAL TRIALS [SEE ADVERSE REACTIONS]. ARRHYTHMIAS OCCURRED IN 1% OF 1,476 PATIENTS WHO RECEIVED IMBRUVICA IN CLINICAL TRIALS. THESE EVENTS HAVE OCCURRED PARTICULARLY IN PATIENTS WITH CARDIAC RISK FACTORS, HYPERTENSION, ACUTE INFECTIONS, AND A PREVIOUS HISTORY OF CARDIAC ARRHYTHMIAS [SEE ADVERSE REACTIONS].

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [See Dosage and Administration (2.2) in Full Prescribing Information].

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

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

SECOND PRIMARY MALIGNANCIES: OTHER MALIGNANCIES (10%), INCLUDING NON-SKIN CARCINOMAS (4%), OCCURRED AMONG THE 1,476 PATIENTS WHO RECEIVED IMBRUVICA IN CLINICAL TRIALS. THE MOST FREQUENT SECOND PRIMARY MALIGNANCY WAS NON-MELANOMA SKIN CANCER (6%).

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR IMBRUVICA® (ibrutinib)

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system event; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively. The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA in the clinical trials [see Adverse Reactions]. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 22% of patients; grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA. Grade 3 or greater ventricular tachycardias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias [see Adverse Reactions].

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Dosage and Administration (2.2) in Full Prescribing Information].

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

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

SECOND PRIMARY MALIGNANCIES: OTHER MALIGNANCIES (10%), INCLUDING NON-SKIN CARCINOMAS (4%), OCCURRED AMONG THE 1,476 PATIENTS WHO RECEIVED IMBRUVICA IN CLINICAL TRIALS. THE MOST FREQUENT SECOND PRIMARY MALIGNANCY WAS NON-MELANOMA SKIN CANCER (6%).
**IMBRUVICA® (ibrutinib)**

† One patient death due to histiocytic sarcoma.

5.3 months in RESONATE in patients with previously treated CLL/SLL.

...below in Tables 3 and 4 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months.

...vs 3% in the ofatumumab arm) occurred in patients.

...vs 2% in the IMBRUVICA arm.

...and neutropenia (8% in the IMBRUVICA arm).

...order in the IMBRUVICA arm.

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

* Includes multiple ADR terms

† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

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

**Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102**

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

* One patient death due to histiocytic sarcoma.

**Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102**

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

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

**Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE**

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>13</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>10</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Contusion</td>
<td>11</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
<td>10</td>
</tr>
</tbody>
</table>

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

**Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE**

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**RESONATE-2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 7.1 months in RESONATE-2.**
Includes multiple ADR terms.

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Rash*</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

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.

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>38</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (1% in the IMBRUVICA arm vs 3% in the chlorambucil arm) and neutropenia (11% in the IMBRUVICA arm vs 12% in the chlorambucil arm) occurred in patients.

Table 7: 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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + BR (N=287)</th>
<th>Placebo + BR (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Bruising*</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=137)</th>
<th>Placebo + Obinutuzumab (N=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>35</td>
<td>31</td>
</tr>
</tbody>
</table>

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.

† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

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

iLLUMINATE: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.
**IMBRUVICA® (ibrutinib)**

**Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in ILLUMINATE (continued)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>33</td>
<td>1</td>
<td>23</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>13</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25</td>
<td>2</td>
<td>58</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage†</td>
<td>25</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>17</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
<td>26</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
<td>17</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>16</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin infection†</td>
<td>13</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* Includes multiple ADR terms
† Includes one event with a fatal outcome.

**E1912: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.**

**Table 9: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912 (continued)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fluorouracil + Cyclophosphamide + Rituximab (N=158)</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>61 (5)</td>
<td>35 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>41 (5)</td>
<td>10 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53 (4)</td>
<td>27 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>40 (1)</td>
<td>64 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>22 (1)</td>
<td>8 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>19 (2)</td>
<td>10 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting†</td>
<td>18 (2)</td>
<td>28 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>49 (4)</td>
<td>29 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising†</td>
<td>36 (1)</td>
<td>4 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>42 (19)</td>
<td>22 (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage†</td>
<td>31 (2)</td>
<td>8 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>40 (1)</td>
<td>27 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (1)</td>
<td>13 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripher neuropathy</td>
<td>19 (1)</td>
<td>13 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>32 (0)</td>
<td>25 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22 (2)</td>
<td>21 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>29 (1)</td>
<td>19 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin infection†</strong></td>
<td>16 (1)</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>19 (1)</td>
<td>4 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>24 (1)</td>
<td>17 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>16 (1)</td>
<td>19 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* Includes multiple ADR terms
† Includes one event with a fatal outcome.

**Table 10: Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fluorouracil + Cyclophosphamide + Rituximab (N=158)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53 (30)</td>
<td>70 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43 (7)</td>
<td>69 (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26 (0)</td>
<td>51 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38 (1)</td>
<td>17 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>20 (2)</td>
<td>15 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>25 (3)</td>
<td>23 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria
IMBRUVICA® (ibrutinib)

DRUG INTERACTIONS

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

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

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

USE IN SPECIFIC POPULATIONS

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

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the general population is unknown. In the P. gondii (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA compared to patients in the control arm. The incidence of ischemic cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack (all grades) were 0.4% and Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 24% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,605 of these patients, the median time to first onset was 30 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 58) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 12% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3).

Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 617) versus 105 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analyzed. The median treatment duration was 51 months (range, 0 to 98 months) for CLL/SLL, 11 months (range, 0 to 97 months) for MCL, and 47 months (range, 0 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%.

Postmarketing Experience: The following adverse reactions have been identified during postapproval 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.

- Headache: headache (all grades), photophobia, and/or dizziness
- Vomiting: nausea, anorexia, and/or diarrhea
- Abdominal pain: cramps, abdominal discomfort (all grades), flatulence, and/or diarrhea
- Gastrointestinal: constipation, decreased appetite, eructation, and/or melena
- Nervous system: headache, dizziness, fatigue, and/or somnolence
- Psychiatric: anxiety, depressed mood, and/or insomnia
- Hematologic: anemia, neutropenia, thrombocytopenia, and/or hemolytic anemia
- Cardiac: angina, myocardial infarction, and/or heart failure
- Respiratory: dyspnea, cough, and/or upper respiratory tract infection
- Skin: rash, pruritus, and/or alopecia

Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 5.4% versus 4.8% and of Grade 3 or greater was 0.4% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack (all grades) were 0.4% and Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

The following adverse reactions have been always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
IMBRUVICA® (ibrutinib)

Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

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

PATIENT COUNSELING INFORMATION

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

- **Hemorrhage:** Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].

- **Infections:** Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].

- **Cardiac arrhythmias and cardiac failure:** Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema [see Warnings and Precautions].

- **Hypertension:** Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].

- **Second primary malignancies:** Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].

- **Tumor lysis syndrome:** Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].

- **Embryo-fetal toxicity:** Advise women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations].

Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations, Nonclinical Toxicology (13.1) in Full Prescribing Information].

- **Lactation:** Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose [see Use in Specific Populations].

Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].

Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].

Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085

and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent http://www.imbruvica.com

IMBRUVICA® is a registered trademark owned by Pharmacyclics LLC

© Pharmacyclics LLC 2020
© Janssen Biotech, Inc. 2020

PRC-07288
CEACAM5 Joins a Growing Menu of Emerging Lung Cancer Targets

by ANITA T. SHAFFER

AFTER NEARLY 2 DECADES of successfully developing therapies directed at molecular aberrations in non–small cell lung cancer (NSCLC), investigators are exploring a new generation of novel targets, including some not specifically associated with driver mutations. One of these emerging targets is carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5), a glycoprotein implicated in a variety of oncogenic activities.

CEACAM5 is overexpressed on the surface of multiple solid tumors, including in about 20% of patients with NSCLC adenocarcinoma, but is not found in normal lung tissue. This makes CEACAM5 a potentially attractive therapeutic target, although efforts to design lung cancer drugs aimed at the protein have been limited.

Currently, tusamitamab rasantinse (SAR408701), an antibody-drug conjugate (ADC), is the most advanced novel agent in clinical testing targeting CEACAM5 specifically in patients with NSCLC, according to a search of ClinicalTrials.gov. Tusamitamab rasantinse has entered phase 3 development in the CARMEN-LC03 trial (NCT04154556), in which investigators are comparing the drug with docetaxel in patients with metastatic nonsquamous NSCLC (NSQ-NSCLC) whose disease has progressed after prior therapy and whose tumors express CEACAM5 at 2+ intensity on at least 50% of the tumor cell population via immunohistochemistry (IHC) testing.

The exploration of new targets such as CEACAM5 would represent another stage in the development of therapies for subsets of patients in NSCLC. Experts in lung cancer and precision medicine discussed the most recent data for some of the novel agents directed at these emerging targets during Molecular Targets on the Horizon in Non–Small Cell Lung Cancer OncLive® Scientific Interchange & Workshop, a panel discussion held on May 25, 2021.

Since the FDA approved the first EGFR-targeted tyrosine kinase inhibitor, gefitinib (Iressa), in 2003, the list of noteworthy genomic alterations in NSCLC has grown to 14, according to the European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets. The FDA has now approved drugs for 9 of these targets, noted program moderator Paul A. Bunn Jr, MD, a 2014 Giants of Cancer Care® award winner in the lung cancer category. Moving forward, novel targets that may be relevant based on protein subtyping include CEACAM5, HER2, HER3, TROP-2, MET, and SHP2.

“Many of these [newer] targets are not driver alterations, and thus they’re often targeted not by tyrosine kinase inhibitors but by antibodies or antibody-drug conjugates that identify the target and attack the target, which is somewhat different from the tyrosine kinase inhibitors that have been developed for what we canister as targeted or molecular therapy at the moment,” said Bunn, the James Dudley Chair in Cancer Research and a distinguished professor of medicine–medical oncology at the University of Colorado School of Medicine in Aurora.

With ADCs, the question of what is driving the malignancy may be different from what it is with the identification of an oncogenic driver, panel member Tejas Patil, MD, said. “It’s less important, or maybe we can have a discussion about the relative importance of this—whether the protein expression isn’t [in and] of itself a driver, but rather whether it’s a target that’s appropriate for an antibody-drug conjugate,” said Patil, an assistant professor of medicine–medical oncology at the University of Colorado School of Medicine. “What’s really important is trying to define some kind of
proteins anchored to the cell membrane, CEACAMs 5,6,7, and 8 are attached to the cell surface through glycoposphatidylinositol, whereas 6 others attach through transmembrane domains. Each member has an N domain and 0 to 6 constant C2-like immunoglobulin domains, with CEACAM5 having the most C2-like domains (FIGURE). 6

Investigators have associated CEACAMs with complex biological functions during cancer progression, metastasis, angiogenesis, and inflammation. 3 More than 20 years ago, results of experiments involving cell lines showed that CEACAM5 overexpression inhibits anoikis, a process important to the apoptosis of cancer cells. 1,9 Moreover, results of prior studies have shown that CEACAM5 is expressed in about 90% of gastrointestinal, colorectal, and pancreatic cancers and in 50% of breast cancer samples. 1

In 2020, Zhang et al published findings from analyses of CEACAM5 expression and activity in NSCLC tissue, cell lines, and mice using quantitative reverse transcription polymerase chain reaction and IHC testing. They found that CEACAM5 stimulated cancer progression in NSCLC through cell proliferation and migration via the p38-SMAD2/3 signaling pathway. 1

Further, investigators used IHC to characterize CEACAM5 expression in tumor issue from 87 patients treated at Linyi Central Hospital in China and correlated the samples with clinicopathological features (TABLE). They found that CEACAM5 expression via IHC testing was significantly associated with tumor stage (P = .022), lymph invasion (P = .002), and histological grade (P = .002). Of note, CEACAM5 expression was not significantly associated with smoking history (P = .147). 1

The findings also demonstrated differences in the extent of cells that positively stained for CEACAM5 on IHC testing, graded as 0 for no positively stained cells, 1 for 1% to 30%, 2 for 31% to 80%, and 3 for 81% or more. Staining indices of less than 3 were rated as low expression, whereas those that were 3 or higher were labeled high expression. 1

In another analysis, CEACAM5 was detected in 38% of lung adenocarcinoma samples (N = 58) and 20% of squamous cell samples (N = 143), but expression differed

### TABLE. CEACAM5 Correlation With Clinicopathological Features in NSCLC Study 1

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>CEACAM5 expression; number of patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>52</td>
<td>16</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Smoker</td>
<td>59</td>
<td>18</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>T3/4</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Lymph invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>N1 or N2</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>Poor</td>
<td>31</td>
<td>6</td>
</tr>
</tbody>
</table>

CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; N, lymph nodes; NSCLC, non–small cell lung cancer; T, tumor size and extent.


HISTORY AS A BIOMARKER

Although recent findings have made CEACAM5 a therapeutic target for NSCLC, the protein has a long history as a biomarker. In 1965, investigators discovered carcinoembryonic antigen (CEA) as a marker for colorectal cancer (CRC), and it has since become widely used for the detection and monitoring of that malignancy. 6 The Centers for Medicare & Medicaid Services also accepts serum CEA assays for monitoring responses to therapy in a range of cancers, including stomach, esophageal, pancreatic, lung, and breast cancers. 7

Initially, CEA was thought to be restricted to fetal expression and malignancy but was later identified in normal adult tissue of the appendix, bone marrow, colon, gallbladder, stomach, and urinary bladder. 3,5

The development of DNA sequencing and monoclonal antibody technologies has enabled a more intricate understanding of CEA as CEACAMs, a family of 12 glycosylated proteins that belong to the immunoglobulin supergene family. 3,6 Of these, only CEACAM5, which also is referred to as CEA, has been accepted as a marker for cancer and recurrence, 4 although CEACAM1 and CEACAM6 also have potential as markers for other malignancies. 5,8

The continued exploration of CEACAMs has revealed that the family members share certain similarities in structure and function but also have differences. Although all members have a long history as a tumor biomarker. In 1965, investigators discovered carcinoembryonic antigen (CEA) as a marker for colorectal cancer (CRC), and it has since become widely used for the detection and monitoring of that malignancy. 6 The Centers for Medicare & Medicaid Services also accepts serum CEA assays for monitoring responses to therapy in a range of cancers, including stomach, esophageal, pancreatic, lung, and breast cancers. 7

Initially, CEA was thought to be restricted to fetal expression and malignancy but was later identified in normal adult tissue of the appendix, bone marrow, colon, gallbladder, stomach, and urinary bladder. 3,5

The development of DNA sequencing and monoclonal antibody technologies has enabled a more intricate understanding of CEA as CEACAMs, a family of 12 glycosylated proteins that belong to the immunoglobulin supergene family. 3,6 Of these, only CEACAM5, which also is referred to as CEA, has been accepted as a marker for cancer and recurrence, 4 although CEACAM1 and CEACAM6 also have potential as markers for other malignancies. 5,8

The continued exploration of CEACAMs has revealed that the family members share certain similarities in structure and function but also have differences. Although all
markedly from weak to very strong expression. Like any protein, the cell surface expression, if you use an IHC test, can be weak, moderate, or strong,” Bunn noted during the OncLive program. “Among the expressions, if you use an IHC test, can be

Among the participants who received tusamitamab ravtansine, the proportion score, ≥ 50%) and in participants whose tumors express PD-L1 (tumor expression of 2+ or greater intensity in 50% or more of the tumor cell population. 16 One of the few agents moving forward is cibisatamab (RG7802; RO6958688), a bispecific antibody that targets CEACAM5 and CD3. Roche is testing cibisatamab in patients with metastatic CRC with high CEACAM5 expression in combination with the PD-L1 inhibitor atezolizumab (Tecentriq) in a phase 1/2 Morpheus Lung umbrella study (NCT03337698), in both patients who have not received prior systemic therapy and whose tumors express PD-L1 (tumor proportion score, ≥ 50%) and in participants whose disease has progressed after prior chemotherapies. 2

**Tusamitamab ravtansine**

Sanoﬁ is leading the ﬁeld in developing therapies directed at CEACAM5 with tusamitamab ravtansine. The ADC comprises a humanized antibody highly selective for CEACAM5, a cytotoxic payload of maytansinoid DM4, and a cleavable linker that remains stable in plasma. The antibody portion of tusamitamab ravtansine binds to the extracellular domain of CEACAM; the ADC is then internalized in the tumor cell and DM4 is released, resulting in inhibition of microtubule activity followed by cell cycle arrest and apoptosis. 2

After demonstrating encouraging signals in preclinical experiments, tusamitamab ravtansine was evaluated in a first-in-human phase 1 study (NCT02187848) in 31 patients with CEACAM5-positive malignancies, including 18 with CRC, 7 with gastric cancer, 3 with gastroesophageal junction cancer, and 1 each with esophageal, pancreatic, and breast cancers. Participants were treated with tusamitamab ravtansine across 8 dose levels from 5 to 150 mg/m². 11

Frequent adverse effects (AEs) included fatigue/asthenia (32%), nausea, neuropathies, decreased appetite (26% each), and diarrhea, constipation, and keratopathy (23% each). Five patients experienced dose-limiting toxicities of grade 3 keratopathy, which was reversible. Investigators concluded that the agent has a manageable safety proﬁle and proceeded to open expansion cohorts for patients with CRC, lung cancers, and gastric cancer with maximum-tolerated dose (MTD) defined as 100 mg/m² every 2 weeks. 11

As the study has progressed, tusamitamab ravtansine results have been most promising in NSQ-NsCLC. Investigators reported interim data at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting for patients with locally advanced or metastatic NSQ-NsCLC with CEACAM5 expression of 2+ or greater intensity in 50% or more of the tumor cell population. Participants received tusamitamab ravtansine at the MTD. 15

The findings showed an overall response rate (ORR) of 25.0% (90% CI, 14.70%-39.20%) in 8 of 32 evaluable patients, all partial responses (PRs). Additionally, 12 patients had stable disease (SD; 37.5%) and 12 had progressive disease (PD; 37.5%). The most prevalent all-grade treatment-related AEs in the safety population (N = 38) included keratitis (23.7%), keratopathy (15.8%), and diarrhea (15.8%). Treatment-emergent AEs (TEAEs) of any grade led to dose modiﬁcation in 31.6% of patients, including 7.9% with grade 3 or greater events. Grade 1/2 keratopathy was cited as the dose modiﬁcation reason for 5 patients (13.2%). 15

At the 2020 ASCO Virtual Scientific Program, investigators reported updated safety and efﬁcacy data for 92 patients with NSQ-NsCLC treated during the dose-expansion phase of the study. Findings were not reported for small cell lung cancer, gastric cancer, and CRC cohorts. In NSQ-NsCLC, data were stratified by CEACAM5 levels into high expressors, with IHC of 2+ or greater intensity on 50% or more of tumor cells, and moderate expressors, with an IHC of 2+ or more on at least 1% to less than 50% of cells. 16

In all, 64 patients were categorized as high expressors and 28 were moderate expressors. The median age was 61.5 years (range, 41-91) for the high expressors and 64.5 years (range, 31-73) for the moderate expressors. Both groups had a median of 3 prior therapies for advanced disease.

The ORR was markedly higher among the high expressors at 20.3% (95% CI, 12.27%-31.71%) compared with the moderate expressors at 7.1% (95% CI, 1.98%-22.65%); all responses in both groups were PRs. The SD and PD rates, respectively, were 43.8% and 32.8% for high expressors and 53.6% and 35.7% for moderate expressors. The median duration of response was 5.6 months (range, 2.0-24.6) among high expressors and was not calculated (range, 3.9-7.3 months) in the moderate expressors. 16

In the safety analysis, pooled data from both NSQ-NsCLC cohorts showed that the incidence of any-grade TEAEs was 100%, including 51.1% for effects of grade 3 or greater severity. These effects included all-grade corneal AEs of keratopathy or keratitis (38.0%), asthenia (37.0%), peripheral neuropathy (27.2%), and dyspnea (21.7%), with grade 3 or greater incidence of 10.9%, 4.3%, 1.1%, and 10.9%, respectively. Additionally, all-grade anemia of 75.8% and thrombocytopenia of 12.2% were reported, with grade 3 or greater incidence of 2.2% and 0%, respectively. 16

During the OncLive Scientific Interchange & Workshop program, panelists discussed the study findings and the TEAEs. In terms of
of ORRs, Bunn noted that the data followed the pattern of higher responses among patients with higher CEACAM5 expression, although he asked whether the ORR among patients with moderate expression warranted further study in that population.

Concerning safety, Bunn noted that the data showed dyspnea was “fairly common,” whereas hematologic toxicity was relatively low. “There was an interesting toxicity with this agent—the keratopathy and keratitis, which is quite different,” Bunn said. “Because the payload is a maytansinoid, peripheral neuropathy was far more common with this ADC than with [other] ADCs we talked about.”

At the same time, Bunn observed that investigators reported ocular events related to the treatment were reversible. For 80% of the patients affected, ocular events first presented within the first 4 cycles of treatment. The condition was manageable with dose delay and/or dose reduction, with a median time to recovery of 18.5 days (range, 2–82). In all, 25 patients had corneal TEAEs leading to dose modification, with only 1 patient (1.1%) permanently discontinuing therapy.16

In light of the response rate among high CEACAM5 expressors, investigators hypothesize that tusamitamab ravidansine may improve outcomes for patients who have progressed after other therapies, Bunn said.

In CARMEN-LC03, investigators are seeking to randomize approximately 554 patients 1:1 to either tusamitamab ravidansine administered intravenously at the MTD dose or docetaxel at 75 mg/m² every 3 weeks. Eligible patients must have metastatic NSQ-NSCLC with at least 1 measurable lesion by RECIST v1.1 criteria and disease progression after platinum-based chemotherapy and immune checkpoint inhibitor therapy.

Participants also must have CEACAM5 expression of IHC 2+ or greater intensity in at least 50% of the tumor cell population. Patients will first be prescreened through analysis of archival or fresh biopsy tumor tissue, and those with CEACAM5 expression of 2+ or 3+ intensity on at least 50% of tumor cells will be further screened. Investigators expect they will have to prescreen about 3250 patients to identify 650 potential participants for further screening before they can reach full enrollment.2

The primary end points are progression-free survival and overall survival. Secondary end points include ORR, response duration, and incidence of treatment-related AEs.

One of the panel members, Edgardo S. Santos, MD, said he could see the rationale of testing tusamitamab ravidansine as second-line therapy after progression on docetaxel and immunotherapy but that he would have liked to have seen higher SD rates heading into a phase 3 trial.

Santos, a medical oncologist at Florida Precision Oncology in Aventura, also noted that he usually uses a combination of docetaxel and ramucirumab (Cyramza) as a second-line option. That combination is becoming a standard of care, panelist David R. Gandara, MD, a 2017 Giants of Cancer Care® award winner in the lung cancer category, observed. “There is some evidence…that this regimen or docetaxel by itself is more effective after immunotherapy,” said Gandara, professor emeritus and director of the Thoracic Oncology Program at the University of California, Davis, Comprehensive Cancer Center.

Investigators are evaluating tusamitamab ravidansine in other lung cancer settings. In the phase 2 CARMEN-LC04 study (NCT04394624), tusamitamab ravidansine is being tested in combination with ramucirumab in patients with CEACAM5-positive NSQ-NSCLC who previously received platinum-based chemotherapy and an immune checkpoint inhibitor.

In the phase 2 CARMEN-LC05 study (NCT04324689), the drug is being evaluated in combination with the PD-1 inhibitor pembrolizumab (Keytruda) with and without cisplatin or carboplatin vs pembrolizumab monotherapy in patients with advanced or metastatic CEACAM5-positive, PD-L1-positive NSQ-NSCLC who have not received prior systemic chemotherapy or immunotherapy.

Additionally, Sanofi has launched the phase 2 CARMEN-BT01 trial (NCT04659603) of tusamitamab ravidansine in patients with CEACAM5-positive metastatic breast or pancreatic cancers. ■

For a full list of references, see the article at OncLive.com.

Molecular Targets on the Horizon in Non–Small Cell Lung Cancer OncLive® Scientific Interchange & Workshop

PROGRAM

9 lung cancer experts discuss new data on emerging targets

TARGETS

- Antibody-drug conjugates directed at CEACAM5, HER2 and HER3, and TROP-2
- KEAP1/NRF2 mutations
- SHP2 inhibition
- TIGIT immune checkpoint

FACULTY

Moderator

Paul A. Bunn Jr, MD
University of Colorado School of Medicine

Panelists

Joshua Bauml, MD
Perelman School of Medicine
University of Pennsylvania

Shirish M. Gadgeel, MD
Henry Ford Hospital

Justin F. Gainor, MD
Massachusetts General Hospital

David R. Gandara, MD
University of California Davis
Comprehensive Cancer Center

Ramaswamy Govindan, MD
Washington University School of Medicine in St Louis

Tejas Patil, MD
University of Colorado School of Medicine

Carolyn J. Presley, MD, MHS
The Ohio State University Comprehensive Cancer Center–James

Edgardo Santos, MD
Florida Precision Oncology

To watch online, visit bit.ly/3IEx5SU
NTRK- and RET-Targeted Agents Reshape Solid Tumor Landscape

by CHRISTINA T. LOGUIDICE

UNDERSTANDING THE ONCOGENIC DRIVERS behind a cancer is taking on increasing importance as more effective agents targeting specific gene aberrations continue to emerge. Two classes of precision agents that have recently had drugs come onto the market include tropomyosin receptor kinase inhibitors (TRKIs) and RET inhibitors, which have been shown to be highly effective in treating patients with tumors harboring NTRK and RET fusions and mutations, respectively.

During a recent OncLive Peer Exchange®, a panel of experts discussed several TRKIs and RET inhibitors that are reshaping the treatment landscape for the patients who are candidates for these treatments and shared their experience using these agents in their own practices. “Biomarker-driven treatment is here to stay, and we’re going to be continuing to evolve our treatment and involve our patients in these therapies,” Lori Wirth, MD, said.

TRKIs FOR NTRK FUSION–POSITIVE SOLID TUMORS

“The first NRTKI gene fusion was discovered as an oncogene in 1982 in colon cancer. It only took 35 years to then develop a therapy, or therapies, that are NRTK directed,” Benjamin P. Levy, MD, said.

Currently, 2 TRKIs are approved for solid tumors with NTRK gene fusions: larotrectinib (Vitrakvi) and entrectinib (Rozlytrek). With these treatments available, Levy emphasized the importance of testing for these fusions (SNAPSHOT 1). “You need to cast that wide net in the lake. Then you can identify these fusions, and these patients can go on to genotype-directed therapy with NRTK inhibition,” he said.

Larotrectinib

On November 26, 2018, larotrectinib became the first NRTK-directed therapy to receive accelerated approval from the FDA and the second agent to receive tissue-agnostic approval for the treatment of cancer. Approval was based on data from the first 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion enrolled across 1 of 3 multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). “Patients [in these trials] were 6 months all the way to 70 years of age, [so the studies] featured a wide range of patients with different ages and tumor types. These patients were highly pretreated, with about one-third having received 3 or more lines of therapy,” Levy said.
NTRK gene fusions were identified using next-generation sequencing (NGS) or fluorescence in situ hybridization (FISH). In 3 pediatric patients with infantile fibrosarcoma, NTRK fusions were inferred based on documentation of ETV6 translocation by FISH. The objective response rate (ORR) was 75% (95% CI, 61%-85%).1 “The drug was active regardless of fusion type, tumor type, or age,” Levy said, noting that later studies of larotrectinib also showed meaningful responses in patients with brain metastases.

Entrectinib
On August 15, 2019, the FDA granted accelerated approval to entrectinib for adults and pediatric patients 12 years and older with solid tumors harboring an NTRK gene fusion without a known acquired resistance mutation, are metastatic, or in which surgical resection is likely to result in severe morbidity who have progressed following treatment or have no satisfactory standard therapy options.2 Entrectinib also received approval as a treatment for adults with metastatic ROSI-positive non–small cell lung cancer (NSCLC).

Approval in patients with NTRK gene fusions was based on data from the first 54 patients with NTRK gene fusion enrolled across 1 of 3 multicenter, open-label, single-arm clinical trials: ALKA-372-001 (NCT02097810), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267).2 The ORR was 57% (95% CI, 43%-71%).

“These responses are durable, and there are intracranial responses as well,” Levy said, noting that this agent was designed to cross the blood-brain barrier.

Deciding between agents
In addition to the basket studies, larotrectinib and entrectinib have been evaluated in a variety of patient subsets, including those with sarcomas, thyroid cancer, and NSCLC. “We do not have any cross-trial comparisons…I do not know if I would necessarily think there is a specific advantage of one over the other,” Levy said, explaining that both are reasonably well tolerated.

In the sarcoma setting, Jonathan Trent, MD, PhD, said he has not “really seen any marked toxicity problems” that would preclude him from prescribing either of these medications. He said that both are very well tolerated but that his clinic uses a lot of tyrosine kinase inhibitors and has become adept at aggressively managing adverse effects (AEs). Above all, he encouraged oncologists to be on the lookout for the NTRK translocations in their patients with sarcoma, noting they can be found in up to one-third of patients with spindle cell sarcoma or undifferentiated pleomorphic sarcoma and occur with varying frequencies in other subtypes, including gastrointestinal stromal tumors (GISTs), malignant peripheral nerve sheath tumors, chondrosarcomas, and angiosarcomas.

When it comes to treating patients with thyroid cancer harboring NTRK fusions, Wirth said her go-to drug is larotrectinib because the data are more robust and have been highly validated.
favorable. She explained that results of a small study presented at the European Society for Medical Oncology Virtual Congress 2020 from Cabanillas et al showed an ORR of 90% for patients with differentiated thyroid cancer (n = 21). Based on the data, she asked the other panelists “How can you not offer it?” She noted, however, that the ORR was significantly lower in the patients with anaplastic thyroid cancer (n = 7), with an ORR of only 29%.

Wirth proceeded to describe a case report in the New England Journal of Medicine that showed promise using larotrectinib as a combination treatment. In the case report, larotrectinib enabled radioactive iodine uptake in a 64-year-old woman with a 34-year history of papillary thyroid cancer with synchronous lymph node and lung metastases. “On larotrectinib, the patient was converted from being iodine refractory—not taking up any radioactive iodine—to taking up radioactive iodine. This suggests that if we block the regulated pathways with an NRTK inhibitor in these patients with NRTK fusions, we may be able to redifferentiate those patients and treat them with a combination of drugs, like larotrectinib and radioactive iodine,” she said.

Wirth anticipates more such case reports being published in the future because clinical trials are difficult to conduct in this setting. “We would need to do a trial with numerous centers even to get a small number of patients,” she said.

In patients with NTRK fusion–positive lung cancer, Jyoti D. Patel, MD, said she is prescribing more larotrectinib but is also using “a lot of entrectinib to treat patients with ROS1 fusions.” Overall, she has found both drugs to be well tolerated but noted that patients on entrectinib tend to have a little more fluid retention. Another issue she brought up is resistance, which has been observed with both agents. “It may be that most patients have a good duration of response, but for patients who do develop resistance, it will be interesting in the long run to see if there are any differences in the mutational profiles of patients taking larotrectinib and those taking entrectinib,” she said.

Trent said that thus far, he has found only 1 patient with an acquired resistance. “That

---

**Selpercatinib (Retevmo)**

**Accelerated approval: May 8, 2020**

**Indication:** for the treatment of adult patients with metastatic RET fusion–positive NSCLC, adult and pediatric patients ≥12 years of age with advanced or metastatic RET-fusion–positive MTC who require systemic therapy; adult and pediatric patients ≥12 years of age with advanced or metastatic RET fusion–positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

**Efficacy data:** LIBRETTO-001 (NCT03157128)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Selpercatinib (n = 39)</th>
<th>Selpercatinib treatment–naïve RET-fusion–positive MTC (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>85% (70%-94%)</td>
<td>73% (62%-82%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>85%</td>
<td>61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Selpercatinib RET-fusion–positive thyroid cancer (n = 19)</th>
<th>Selpercatinib systemic therapy–naive, RET fusion–positive thyroid cancer (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>85% (70%-94%)</td>
<td>100% (63%-100%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>0%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>85%</td>
<td>88%</td>
</tr>
</tbody>
</table>

**Pralsetinib (Gavreto)**

**Accelerated approval: December 1, 2020**

**Indication:** for the treatment of adult patients with metastatic RET fusion–positive NSCLC; adult and pediatric patients ≥12 years of age with advanced or metastatic RET-fusion–positive MTC who require systemic therapy; adult and pediatric patients ≥12 years of age with advanced or metastatic RET fusion–positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

**Efficacy data:** ARROW (NCT03037385)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pralsetinib RET-fusion–positive NSCLC previously treated with platinum chemotherapy (n = 87)</th>
<th>Pralsetinib treatment–naïve, RET-fusion–positive NSCLC (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>57% (46%-68%)</td>
<td>70%</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>5.7%</td>
<td>11%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>52%</td>
<td>57%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pralsetinib RET-fusion–positive thyroid cancer (n = 55)</th>
<th>Pralsetinib treatment–naïve RET-fusion–positive MTC (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>60% (46%-73%)</td>
<td>66% (44%-82%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>1.8%</td>
<td>10%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>58%</td>
<td>55%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Selpercatinib RET-fusion–positive thyroid cancer (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>89% (52%-100%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>0%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>89%</td>
</tr>
</tbody>
</table>

MTC, medullary thyroid cancer; NSCLC, non–small cell lung cancer.

*Patients were previously treated with cabozantinib or vandetanib.

*Patients were not treated with prior cabozantinib or vandetanib.
seemed to be the result of a mutation in the ATP [adenosine triphosphate] binding pocket of the kinase. This is what we have seen in patients with KIT mutations and patients with GISTs who become resistant to imatinib [Gleevec]. It is going to be interesting to see whether newer generations of TRKIs can overcome this type of resistance,” he said.

TARGETING RET FUSIONS AND MUTATIONS IN SOLID TUMORS

The RET oncogene was first discovered in an NIH3T3 cell line in 1985. One year later, after the Chernobyl accident occurred, RET fusions were identified in children from contaminated regions who developed papillary thyroid cancer; however, RET fusions did not garner clinical interest until 2012, when they were identified as being a driver of NSCLC.

“RET is a juicy target because it is a receptor tyrosine kinase,” Wirth said. She explained that RET fusions are primarily seen in papillary and other thyroid cancers and in a subset of patients with NSCLC, but that they can occasionally be found in other cancers, including pancreatic adenocarcinomas. She also noted that other alterations may be seen, such as germline or somatic RET point mutations, but that these are only thought to be cancer drivers in the setting of medullary thyroid cancer (MTC). “Because RET is not necessarily expressed in other tissues, a point mutation is not going to have any sort of oncogenic effect if it is not expressed to begin with,” she said. In patients with MTC, however, “various RET mutations do cause various degrees of aggressiveness of the cancer,” she explained.

Several drugs with RET activity have been available for some time, including sunitinib (Sutent), vandetanib (Caprelsa), and cabozantinib (Cabometyx), but these are multikinase inhibitors that also have other targets, such as VEGFR2, EGFR, and KDR. Subsequently, the panelists noted that these drugs have a lot of off-target effects that make them more difficult to tolerate and limit the ability to dose escalate. In contrast, the newer RET inhibitors have been designed to just target RET and have been shown to elicit meaningful activity while being better tolerated. Thus far, 2 RET inhibitors have been approved by the FDA: selpercatinib (Retevmo) and pralsetinib (Gavreto) (DRUG SNAPSHOT 2).

Selpercatinib

“Selpercatinib was designed to inhibit all of the RET fusions that we see in NSCLC and other cancers. It was designed to inhibit all known RET mutations seen in MTC. Then it was also designed to head off acquired gatekeeper resistance mutations at the codon V804, which was hypothesized to account for acquired resistance,” Wirth said.

Selpercatinib was granted accelerated approval by the FDA on May 8, 2020, for 3 indications. Approval was based on data from the phase 1/2 multicenter, open-label, multicohort LIBRETTO-001 trial (NCT03157128), the results of which were published in 2 separate articles.

“The primary analysis set concerned patients with RET-mutated MTC who had previously been treated with cabozantinib, vandetanib, or both,” Wirth said. In these patients (n = 55), the ORR was 69% (95% CI, 55%-81%), and the 1-year progression-free survival (PFS) was 82% (95% CI, 69%-90%). When examining the patients with RET-mutant MTC who had not previously received vandetanib or cabozantinib (n = 88), the ORR was 73% (95% CI, 62%-82%) and the 1-year PFS was 92% (95% CI, 82%-97%). In patients with previously treated RET fusion-positive thyroid cancer, the ORR was 79% (95% CI, 54%-94%) and 1-year PFS was 64% (95% CI, 37%-82%). “These responses are all durable. In the primary analysis set, the median duration of response and median PFS were not yet reached by the time of the data maturity for the publications,” Wirth said.

In patients with RET fusion-positive NSCLC (n = 105), the ORR was 64% (95% CI, 54%-73%), with a median duration of response of 17.5 months and 63% of responses ongoing after a median follow-up of 12.1 months.

Among the patients who did not receive previous platinum-based chemotherapy (n = 39), the ORR was 85% (95% CI, 70%-94%), with 90% of the responses ongoing at 6 months. Among the patients with measurable central nervous system metastasis at enrollment (n = 11), the percentage with an objective intracranial response was 91% (95% CI, 59%-100%). “In terms of safety, we see primarily grade 1 and 2 AEs, and these are reversible,” Wirth said. “A small number of patients had QTc prolongation; a couple of patients had grade 3 QTc prolongation.”

Pralsetinib

On September 4, 2020, the FDA granted accelerated approval to pralsetinib for adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA-approved test, and expanded the indication on December 1, 2020. These approvals were based on data from the multicenter, open-label, multicohort ARROW trial (NCT03037385).

“The lung cohort was reported first with the fusions, and [similar to LIBRETTO-001], patients could come on as treatment naïve,” Patel said. In those patients, the ORR was 70% (95% CI, 50%-86%), whereas in those with prior platinum treatment, it was 61% (95% CI, 50%-71%). Complete responses were observed in 11% and 6% of these patient cohorts, respectively. “Remarkably, 100% of patients had some tumor shrinkage. The waterfall plot went across the board,” she said.

Similar findings were observed in the patients with RET fusion-positive MTC. “The response rate was 60% [for patients previously treated with cabozantinib and/or vandetanib], with some complete responses,” Patel said. “The median duration of response, again, was not reached. For patients who were treatment naïve, their response rate was about 82%. Again, we are seeing this broad activity.”

Patel noted that in patients with NSCLC who received pralsetinib or selpercatinib, the toxicity was higher among the patients who received some immunotherapy as part of their previous platinum treatments. “Patients who received platinum alone seemed to tolerate treatment really well. I think we are seeing how that evolves as more patients are treated,” she said.

When asked to compare agents, Levy said they look fairly similar, despite the response rates being slightly higher with selpercatinib. “It is a win to have this embarrassment of riches compared to what we had before,” he said. “I think both are extremely well tolerated and elicit meaningful responses below the neck and above the neck, intracranially.”

For a full list of references, see the article at OncLive.com.
CONNECT WITH PURPOSE

TECENTRIQ is committed to helping you treat patients

Learn more about our FDA-approved indications at TECENTRIQ.com/info