INSIDE

LUNG CANCER
RENAL CELL CARCINOMA
CHRONIC LYMPHOCYLTIC LEUKEMIA
BREAST CANCER
B-CELL LYMPHOMA
GRAFT-VS-HOST DISEASE
MYELOPROLIFERATIVE NEOPLASMS
HEPATOCELLULAR CARCINOMA
PROSTATE CANCER
# Table of Contents

## LUNG CANCER
- 9 Joshua K. Sabari, MD
- 34 Thomas E. Stinchcombe, MD
- 109 Aaron E. Lisberg, MD

## RENAL CELL CARCINOMA
- 19 Rana R. McKay, MD
- 75 Pedro C. Barata, MD, MSc

## CHRONIC LYMPHOCYTIC LEUKEMIA
- 30 Jan A. Burger, MD, PhD

## BREAST CANCER
- 54 Tiffany A. Traina, MD
- 114 Jeffrey Aldrich, MD; Maisey Ratcliffe, MPH; and Manali A. Bhave, MD

## B-CELL LYMPHOMA
- 57 Nina Wagner-Johnson, MD
- 94 Cyrus M. Khan, MD

## GRAFT-VS-HOST DISEASE
- 72 Michael R. Bishop, MD
The Case-Based Roundtable Meetings Spotlight covers a series of oncology education roundtable meetings for practicing oncologists led by expert physicians presenting case-based data across cancer types.

By attending a Targeted Oncology™ Case-Based Roundtable Meeting ("Event"), all participants, attendees, sponsors, and guests ("you") create an agreement between you and Targeted Oncology™ regarding the use and distribution of your image, including but not limited to your name, voice, and likeness ("Image"). By attending the Event, you acknowledge and agree that photographs, video, and/or audio recordings may be taken of you and you grant permission to Targeted Oncology™ (and its agents) to utilize, in perpetuity, your Image in any electronic or print distribution, or by other means herein created, both now and in the future, for any lawful purpose as determined by Targeted Oncology™.

Interestingly, when you look at prospective studies [in lung cancer], the response rate to cisplatin does not seem to be all that much different from carboplatin.”

—JOSHUA K. SABARI, MD

The new web exclusive! Read more meeting summaries like the ones in this issue in the new Case-Based Roundtable Series on TargetedOnc.com. Hear expert insights and evaluation of therapies for various clinical case profiles.

Dive into the series now!

Scan the QR code to check out a recent series: Later-Line Choices for Patients With Metastatic TNBC

TargetedOnc.com/link/1573
Visit ErleadaHCP.com

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)

INDICATIONS
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

1. Metastatic castration-sensitive prostate cancer (mCSPC)
2. Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION WARNINGs AND PRECAUTIONs
Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA®, and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA® and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) 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.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and 1% 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 (0.2%) treated with ERLEADA®, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event. 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.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. 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.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. 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.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. 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 (8.1, 8.3)].

ADVERSE REACTIONS
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, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
- Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.1%); thrombocytopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%).
- Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.5%). In the SPARTAN study:
ERLEADA® + ADT demonstrated SUPERIOR OS in men with mCSPC vs ADT alone1-3

- Median OS was not reached in the ERLEADA® + ADT arm compared with 52.2 months in the ADT arm. Median follow-up time was 44.0 months3,2
- TITAN primary analysis results: Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053. Median follow-up time was 22.7 months3,2

35%
REDUCTION IN THE RISK OF DEATH IN MEN WITH mCSPC*

HR=0.65. 95% CI: 0.53, 0.79

Visit ErleadaHCP.com for more information about STARTING EARLY WITH ERLEADA® TO HELP HIM LIVE LONGER.1


© Janssen Biotech, Inc. 2022 04/22 cp-293003v1

Permanently discontinue ERLEADA® in 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.

**INDICATIONS**

Start early with ERLEADA® to help him live longer.1

ERLEADA® may help him be there to experience them.1

Help him be there... he never thought he’d see the day.1

**ADVERSE REACTIONS**

- hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1.0%); hypertriglyceridemia ERLEADA® 67% (1.5%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (1.9%), placebo 22% (0.5%)

**Rash** — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area (BSA)) were 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 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 26% 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 1.5% 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

**DRUG INTERACTIONS**

**Effect of Other Drugs on ERLEADA®** — Co-administration of a strong CYP2C9 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (see Dosage and Administration [2.2]).

**Effect of ERLEADA® on Other Drugs**

CYP3A4, CYP2C9, CYP2C19, and UGT Substrates—ERLEADA® is an 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.

P-gp, BCRP, or OATP1B1 Substrates—Avapastatide is a weak inducer of P-glycoprotein (P-gp), 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.

**Drug Interactions**

- Median OS was not reached in the ERLEADA® + ADT arm compared with 52.2 months in the ADT arm. Median follow-up time was 44.0 months3,2
- TITAN primary analysis results: Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053. Median follow-up time was 22.7 months3,2

**Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (i.e., liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchectomy. The dual primary endpoints were overall survival and rPFS.1,2

ADT, androgen deprivation therapy; CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; mCSPC, metastatic castration-sensitive prostate cancer; NE, not estimable; mCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival; TITAN, Targeted Investigational Treatment Analysis of Novel Anti-androgen.
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 2.7% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.9%) 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 2.5% of patients treated with ERLEADA and 1% of patients treated with placebo [see Adverse Reactions]. In the TITAN study, cerebrovascular events occurred in 3% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.9%) 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 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Falls

Falls 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 2.7% of patients treated with ERLEADA and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 933 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 1.5%. The median time to onset of first 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.

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. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were not excluded. 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 not excluded. In the SPARTAN study, four patients (0.8%) treated with ERLEADA, and one patient treated with placebo (0.2%) experienced a seizure. In the TITAN study, one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred in patients receiving ERLEADA. Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), central nervous system events (n=1), heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

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.

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, hyperpigmentation, hot flush, diarrhea, 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 18 months (range: 0.1 to 34 months) in patients who received placebo. Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), central nervous system event (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 (2.3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hyperpigmentation. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred ≥15% in patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>17</td>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>28</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Pruritus</td>
<td>11</td>
<td>0.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

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

Additional adverse reactions of interest occurring in ≥2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3.1% versus 1.9% on placebo), dysgeusia (3.2% versus 0.6% on placebo), and hypothyroidism (3.6% versus 0.6% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia*</td>
<td>17</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values
Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>Placebo N=398</th>
<th>ERLEADA N=803</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site</td>
<td>Fatigue*</td>
<td>39</td>
<td>1.4</td>
<td>28</td>
<td>0.3</td>
<td>44</td>
<td>1.6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia*</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>25</td>
<td>5.2</td>
<td>6</td>
<td>0.3</td>
<td>32</td>
<td>3.7</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>12</td>
<td>0.1</td>
<td>9</td>
<td>0</td>
<td>12</td>
<td>0.9</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Fracture*</td>
<td>12</td>
<td>2.7</td>
<td>7</td>
<td>0.8</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased*</td>
<td>16</td>
<td>1.1</td>
<td>6</td>
<td>0.3</td>
<td>18</td>
<td>1.5</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>25</td>
<td>14</td>
<td>20</td>
<td>12</td>
<td>27</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Hot flush</td>
<td>14</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>18</td>
<td>2.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>20</td>
<td>1.1</td>
<td>15</td>
<td>0.5</td>
<td>21</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>18</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>17</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Includes fatigue and asthenia
* 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
* Includes appetite disorder, decreased appetite, early satiety, and hypophagia
* Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritis (6% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).
**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 rosvuastatin (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 findings from animals and 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]. There are no available data on ERLEADA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥2 times the human clinical exposure (AUC) at the recommended dose [see Data].

**Data**

**Animal Data**
In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar ribs), and small, incomplete ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients.

**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.

**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**

**Adverse Events**

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].

**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.

- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.

- 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].

- Instruct 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 can be harmful to a developing fetus. 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. 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 00787
Manufactured for:
Janssen Products, LP
Horsham, PA 19044
© 2019 Janssen Pharmaceutical Companies cp-50599v7
#### DISCUSSION QUESTION
In general, what are the most common reasons immunotherapy is not used as first-line therapy in patients with ES-SCLC?

**KAPPEL:** [In general], these patients present when they’re sick, and instead of giving the immunotherapy a chance, practitioners go to [palliative] care right from the very beginning.

There’s a line where they’ll treat vs not treat, but if [patients] get a response, it is quickly. So if you’re going to treat them, you’ve got to treat them and keep your fingers crossed.

**SABARI:** Anyone else have issues up front? What are some common reasons for not getting immunotherapy in the frontline setting?

**BLOKH:** If they’re in the hospital, that’s how you meet them for the first time, and you just diagnose them in the hospital. One could give them 1 cycle of a platinum plus etoposide [Toposar] regimen, but after that cycle, they’re going to get out.

One could start giving them the immunotherapy. It shouldn’t really be an impediment at just 1 cycle, but that’s the only time they probably are missing immunotherapy in general.

**KAPPEL:** Yes, but that’s a great question, because 90% of the newly diagnosed patients you see in the hospital get discharged. You do their PET scans and work-up, and they’ll start their treatment 2 to 3 weeks later as an outpatient, and you don’t just have that luxury with these patients.

**SABARI:** We’ve all been consulted on a newly diagnosed SCLC inpatient. What does that look like in your practice? Are you able to get immunotherapy in the inpatient setting?

**SABARI:** I agree with that. I have a hard time even getting into chemotherapy, [because it’s] a lift to get chemotherapy in the hospital through the administrators. We generally have a difficult time getting immunotherapy approved [by insurance],
so I oftentimes will give 1 cycle of carboplatin [Paraplatin] and etoposide [to an] inpatient. And to your point, start cycle 2 in the outpatient setting. Any other barriers to using immunotherapy in the frontline setting?

**MODI:** A related contraindication, [such as] uncontrolled rheumatologic disorders or in HIV with very low CD4 count. Otherwise, I don’t encounter any significant barriers when we’re trying to use the immunotherapy [for patients with] ES-SCLC.

**SABARI:** We worry about contraindications to immunotherapy, [such as] rheumatologic conditions [or] lupus, which we more commonly see in the non–small cell lung cancer [NSCLC] population.

But Dr Modi brought up a great point about HIV, and there’s a lot of prospective data now to support the use of immune checkpoint inhibitors [ICIs], even in patients with HIV, even with low CD4 counts. Although these patients are generally excluded from our clinical trials, there is now prospective data that support safety of these agents in this patient population.

**DISCUSSION QUESTIONS**

- What additional work-up, if any, would you order to inform your treatment recommendation?
- How would you counsel this patient regarding her treatment options? What do you consider the most important points to communicate?

**NIERODZIK:** Well, the most important thing in these patients with ES-SCLC is [similar to patients with] lymphoma. Look at organ dysfunction, [don’t] use cisplatin [Platinol], then you have pretty much what you need to start the patient on chemotherapy.

**SABARI:** So, because of their burden of disease and how sick they are, what agents are you going to use?

**WU:** I agree with Dr Nierodzik. Usually we want to make sure the patient doesn’t have contraindications to certain therapy and make sure renal function is OK.

If a patient doesn’t have an autoimmune disease contraindication, immunotherapy will be preferred if they are treated as an outpatient.

**SABARI:** Agreed. What about PD-L1 expression or molecular testing? Is that important? Does it guide treatment? I know it’s been drilled into our heads multiple times, so is it something you look at in [patients with] SCLC?

**WU:** No, not in SCLC.

**SABARI:** I agree. I oftentimes will not wait for molecular testing here. We know it’s going to be TP53 and RB1 tumor suppressor loss. We don’t wait for PD-L1 expression because it doesn’t guide our treatment. That’s an important point. Immunotherapy is not guided by the PD-L1 expression as it is in NSCLC.

**KAPPEL:** Is there any value to looking at other markers after starting treatment? For NSCLC and other malignancies, do you wait for a FoundationOne panel to come back?

**SABARI:** I obtain tissue [and] plasma next-generation sequencing [NGS] on patients with SCLC. But if you ask me how often I act on it, it’s very low. It’s more of an academic pursuit.

Very rarely—probably in less than 1% of cases—can one identify an EGFR mutation in this population, and this is generally in the never-smoking population, who had a de novo SCLC transformation.

**LI:** If the EGFR mutation was positive, are you treating with a targeted therapy or chemotherapy?

**SABARI:** [Now, in terms of ordering additional work-up], because of transformation, the EGFR inhibitor is not going to be effective, but we’re still going to use platinum and etoposide plus or minus immunotherapy. So NGS is academically helpful. If you’re thinking about the development of new agents in the next 5 to 10 years, protein expression [and] some other markers are going to be very helpful.

Charles Rudin, MD, PhD, has a beautiful paper that was published about 2 years ago from Memorial Sloan Kettering [Cancer Center], looking at 4 different subtypes of SCLC in animal models, but also in human patient–derived xenograft models.¹ We are looking at basketing these patients when we develop new clinical therapies.

There are some markers, [such as] protein and gene expression, that will help guide potential therapeutic development, but in 2022, molecular testing and PD-L1 expression are not useful in this setting. I would not wait for those results in SCLC; it does not generally change the patient outcomes.

**BLOKH:** I order [an] NGS panel on every patient with a solid malignancy I have, because I realize that even if it will not affect first-line therapy, maybe it will affect second-line therapy, or maybe they’ll eventually be a candidate for clinical trial. Now, what’s the point of doing NGS on certain malignancies, where it does not affect management?
Doesn’t it make much better sense on a practical level to do the NGS at progression, then do a send-off? What’s the point? One may get some evolution and some selective pressures from the treatments you’re giving, but you’re still going to do another NGS at progression, so why not just do it at progression for malignancies, where NGS has no effect on initial treatment?

SABARI: Again, in the frontline setting, there is no change in practice with NGS. It’s still done in academic practice. I don’t know whether there’s a great rationale, except for potential development of new strategies in the future. You’re right, maybe it would be more helpful in the recurrent setting.

Generally, with immunotherapy or targeted therapy, you don’t have much selective changes or pressures for driver mutations, but it’s very different when you’re looking at protein expression. We have seen many different portfolios for SCLC post treatment with platinum and a PD-L1 inhibitor.

Polling Question

“What proportion of your patients with ES-SCLC is treatment initiated in the inpatient setting?”

- 25% (2)
- 25% to 50% (1)
- 51% to 75% (1)
- 75% (0)

Total Votes: 4

NIERODZIK: I have a question about doing both plasma and tissue NGS in these patients. I do it sometimes because I’m afraid that the samples are so small that we may not have enough for the tissue for FoundationOne, but what’s the rationale for doing both?

SABARI: For plasma NGS in SCLC, it’s helpful for heterogeneity, but again, it’s not going to change or drive management. Very rarely you get a [fine needle aspiration] when you don’t have enough tissue to make an accurate diagnosis, or there’s complete necrosis [that’s] very poorly differentiated and hard for the cytopathologist to give a diagnosis. In that case, it’s helpful to see RB1 and TP53 loss, which are the hallmarks of SCLC. It just drives our excitement here.

The other important reason is you see combined SCLC and NSCLC, either adenocarcinoma or squamous carcinoma, [approximately] 10% to 15% of the time. That’s where plasma and tissue NGS can help. It changes the prognosis. It also may help later down the road if patients have recurrence, but it does not generally change the frontline management. For the question of tumor heterogeneity, it is particularly useful in a combined picture, but again, it is not going to change management.

Most of us are treating patients in outpatient settings. It’s [uncommon] for us to be treating these patients in the inpatient setting. In the literature, especially from the SEER database literature, [approximately] 50% of patients get their first cycle in the inpatient setting. I agree, it’s [uncommon] in my practice—probably 1 or 2 of every 10 patients with SCLC are started on treatment as inpatients.

Now, for this patient case, how would you counsel this patient? What are you thinking about for her treatment regimen?

LI: I would start chemotherapy and immunotherapy, but I would do [gamma knife], because this is SCLC, and I am concerned a brain mass can progress even on the chemotherapy. The [gamma knife] is a 1-day treatment [and you are done]. I would then give a platinum plus etoposide plus atezolizumab [Tecentriq] as the regimen.

MODI: We usually use [platinum,] etoposide, and atezolizumab. I would do close monitoring for the brain mass and maybe reimage the brain in a couple weeks to make sure it’s not progressing while on the chemotherapy.

CHEUNG: [I would give] etoposide/cisplatin/atezolizumab.

SABARI: Interesting. Dr Cheung is the first to mention cisplatin. Dr Blokh, what are you using in the frontline?

BLOKH: I would not attack that brain lesion, as I think it’s asymptomatic and small. I would give a platinum, etoposide, and immunotherapy. In terms of which platinum, I remember they’d traditionally say if it’s extensive, it’s not curable, so why give cisplatin?

But if cisplatin has better activity and someone has good performance status, is relatively young, their kidneys are young, and everything else is fine, I don’t see any negatives for trying it to see whether you can maximize response.

BRAUNSTEIN: I agree—atezolizumab, carboplatin, [and] etoposide. The question is where you are sequencing the radiation. I would probably start the systemic therapy, then radiation afterward.

DAI: I would start a systemic chemotherapy with etoposide, carboplatin, [and] atezolizumab. I would postpone radiation, because the brain mass is small and the patient is asymptomatic.
**WU:** I probably would do carboplatin, etoposide, durvalumab [Imfinzi]. I thought the data for durvalumab included more patients with asymptomatic brain metastasis.

**SABARI:** That’s the first durvalumab response we’ve heard tonight, which is interesting. Again, it’s controversial and we’ll have that discussion.

**VIVEKANANDARAJAH:** I also would use carboplatin, etoposide, [and] durvalumab in these patients. I thought that because the patient has brain metastasis, it probably means durvalumab has better response in these patients. As far as the brain metastasis, I would watch it and see how the patient is progressing.

**NIERODZIK:** [Because of the brain metastasis], I would use durvalumab if I could get it. I always time the gamma knife, but I usually wind up giving [chemoimmunotherapy] first and getting another image. Unless they’re progressing, then I will do the gamma knife a little further down the line.

**SABARI:** We talked about a platinum agent—whether to use cisplatin or carboplatin. The patient has a brain metastasis—whether to deal with it up front or not. We talked about atezolizumab vs durvalumab; are there any differences here?

**KAPPEL:** For the brain metastasis, I would see how symptomatic or [asymptomatic] they are and discuss with my radiation oncologist, then observation.

**SABARI:** The newest National Comprehensive Cancer Network guidelines for systemic primary therapy in ES disease recommend 4, not 6, cycles [because of] toxicity.

The preferred regimens are carboplatin, etoposide, atezolizumab, followed by atezolizumab maintenance, or carboplatin, etoposide, durvalumab, followed by durvalumab maintenance. Cisplatin is controversial, but I agree with Dr Blokh. If you have someone who has an ECOG performance status of 0 or 1, it does make sense.

Outside the United States, there is significantly more use of cisplatin in the frontline setting. In our patient population, there’s been head-to-head studies of cisplatin, etoposide vs carboplatin, etoposide, and there haven’t been any real differences. Some of the studies—for example, the atezolizumab one—did not allow for cisplatin, whereas the durvalumab regimen did, so there were some slight differences.

I think it’s inferior in 2022 to not offer a PD-L1 inhibitor in the frontline setting. There are regimens that do not use etoposide but use irinotecan [Camptosar], [which is] generally not something we commonly use in the frontline setting here in the United States.

---

**DISCUSSION QUESTIONS**

- What’s your reaction to the updated CASPIAN [NCT03043872] data? How has it changed your practice?
- What would your approach toward the management and follow-up be of this patient at this time?
SABARI: Any experiences, negative or positive, with the durvalumab regimen? Do you think it’s helping patients? Is it doing much more than what we saw with standard carboplatin plus etoposide?

LI: I would say yes. I have a patient who now has used it for 2 years, so using chemotherapy alone would not have lasted as long.

KAPPEL: I don’t go past 4 cycles all that much. It’s also because atezolizumab has the advantage of being the first drug out. The other drugs in the CASPIAN study have got to show significant improvement, which they don’t.

For both studies, and correct me if I’m wrong, if you have brain metastasis, there is no significant improvements with immunotherapy. Is that correct?

SABARI: Sarah Goldberg, MD, MPH, at Yale School of Medicine has shown data for NSCLC with pembrolizumab [Keytruda], for example, showing CNS [central nervous system] activity. But in SCLC, we don’t have much prospective data.

These patients all had treated brain metastasis, so it’s hard to say. But it does look like, in the subset analyses, patients did better with durvalumab than with atezolizumab. But honestly, it is hard to make that conclusion based off the small numbers we have.

CHEUNG: Have they differentiated response rates between cisplatin and carboplatin in the CASPIAN trial?

SABARI: Interestingly, when you look at prospective studies, the response rate to cisplatin does not seem to be all that much different from carboplatin. Then you could also argue that maybe healthier patients are getting cisplatin vs carboplatin. It’s a double-edged question.

This patient went on to develop diarrhea—so immune-mediated colitis—3 to 4 times a day, as well as nausea after the second cycle. Diarrhea is not all that uncommon, right? Again, thinking broadly outside of SCLC, we use PD-1 and PD-L1 inhibitors routinely.

BRAUNSTEIN: It depends on the grade of the diarrhea. Was this patient admitted? It sounds like it was low grade, so I would just rechallenge and monitor the diarrhea.

SABARI: If it’s grade 1 or 2 and you’re able to treat with low-dose steroids, for example, or holding 1 or 2 cycles and then they recover, I oftentimes will retreat. But for grade 3 or 4 adverse events [AEs], I would stop therapy.

We’ve all seen our patients, particularly those who get a CTLA-4 inhibitor, for example, in combination with a PD-1 or PD-L1 inhibitor, who have grade 3 or 4 AEs where you need to use high-dose steroids, infliximab [Remicade], and other agents down the road. I would not feel comfortable retrying [those patients], but I agree with you. Immune-related AEs have become a common scenario in our clinical practice.

For a list of references visit TargetedOnco.com
For adults with intermediate- or high-risk myelofibrosis (MF)

Jakafi and the Jakafi logo are registered trademarks of Incyte.

Indications and Usage

Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.

Important Safety Information

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

WHAT YOU DO TODAY CAN IMPACT THEIR TOMORROW
Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis.

**Indications and Usage**

- Manage thrombocytopenia by reducing the dose or temporarily interrupting.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for stabilized, and then as clinically indicated complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥20%) were diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections.

**References:**


Jakafi and the Jakafi logo are registered trademarks of Incyte. © 2022, Incyte Corporation. MAT-JAK-03732 01/22
**Myelofibrosis**

The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months. An important adverse reaction was thrombocytopenia and anemia (see Table 2).

**Description of Selected Adverse Reactions: Anemia**

In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 0.2 in patients treated with placebo.

**Thrombocytopenia**

In the two Phase 3 clinical studies, in patients who developed grade 2 or higher thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose interruption. The median time to recovery of platelet counts above 50 ×10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens.

**Thrombocytopenia**

Thrombocytopenia, with or without bleeding, occurred in 26% of patients treated with Jakafi and 2% of patients treated with placebo. Table 2 provides the incidence of thrombocytopenia in patients who required discontinuation of treatment because of thrombocytopenia. Thrombocytopenia is a known adverse reaction associated with Jakafi treatment. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 0.2 in patients treated with placebo.

**ADVERSE REACTIONS**

The following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If these symptoms occur, Jakafi should be stopped and Jakafi and evaluate. Herpes Zoster and patients who develop infections should be managed promptly. Use active surveillance and preemptive antiviral therapy for patients who have a history of herpes zoster or are at risk for developing herpes zoster.

**Malignancies**

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. In a successfully treated NMSC), patients who develop a new malignancy should receive active surveillance and preemptive antiviral therapy. See Table 1 for a list of malignancies associated with Jakafi treatment.

**Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment**

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=158)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Worst Grade during Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
<td>Grade 3 (≥ 10%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>International normalized ratios of coagulation factors (INR)</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
</tbody>
</table>

**Grade 3 or 4 Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

- Granulocytes: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Platelets: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Hemoglobin: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Prothrombin: Grade 4 (≥ 3%)
- International normalized ratios of coagulation factors (INR): Grade 4 (≥ 3%)

**Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment**

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=158)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Worst Grade during Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
<td>Grade 3 (≥ 10%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>International normalized ratios of coagulation factors (INR)</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
</tbody>
</table>

**Grade 3 or 4 Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

- Granulocytes: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Platelets: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Hemoglobin: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Prothrombin: Grade 4 (≥ 3%)
- International normalized ratios of coagulation factors (INR): Grade 4 (≥ 3%)

**Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment**

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=158)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Worst Grade during Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
<td>Grade 3 (≥ 10%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>International normalized ratios of coagulation factors (INR)</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
</tbody>
</table>

**Grade 3 or 4 Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

- Granulocytes: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Platelets: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Hemoglobin: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Prothrombin: Grade 4 (≥ 3%)
- International normalized ratios of coagulation factors (INR): Grade 4 (≥ 3%)

**Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment**

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=158)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Worst Grade during Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
<td>Grade 3 (≥ 10%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
<tr>
<td>International normalized ratios of coagulation factors (INR)</td>
<td>Grade 4 (≥ 3%)</td>
</tr>
</tbody>
</table>

**Grade 3 or 4 Laboratory Abnormalities in the Open-label, Single-arm Phase 3 Studies**

- Granulocytes: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Platelets: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Hemoglobin: Grade 3 (≥ 10%) and Grade 4 (≥ 3%)
- Prothrombin: Grade 4 (≥ 3%)
- International normalized ratios of coagulation factors (INR): Grade 4 (≥ 3%)
of treatment because of thrombocytopenia occurred in < 1% of patients receiving Jakafi and < 1% of patients receiving control regimens. Patients with a platelet count of 100 × 10^9/L to 200 × 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 × 10^9/L (17% versus 7%). Neutropenia in the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

### Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=151)</th>
<th>Placebo (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 3 4% 36%</td>
<td>Grade 3 4% 14%</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 4 16%</td>
<td>Grade 4 16%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 4% 36%</td>
<td>Grade 3 4% 14%</td>
</tr>
</tbody>
</table>

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

### Additional Data from the Placebo-Controlled Study

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

### Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥ 5% of Patients on Jakafi in the Open-label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=151)</th>
<th>Placebo (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Headache</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Rash</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Cough</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>URI</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

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

### Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 4 1%</td>
<td>Grade 4 1%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 4 1%</td>
<td>Grade 4 1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

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

### Acute Graft-Versus-Host Disease

In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for aGVHD failing treatment with steroids or with or without immunosuppressive drugs [see Clinical Studies (14.4) in Full Prescribing Information]; sixty-five patients crossed over from best available therapy available with Jakafi. Of a total of 230 patients treated with Jakafi. The median duration of exposure to Jakafi for the study was 49.7 weeks (range, 0.7 to 144.9 weeks) in the Jakafi arm. One hundred and nine (47%) patients were on Jakafi for at least 1 year. There were five fatal adverse reactions to Jakafi, including 1 from toxic epidermal necrolysis and 4 from neutropenia, anaemia and/or thrombocytopenia. An adverse reaction resulting in treatment discontinuation occurred in 18% of patients treated with Jakafi. An adverse reaction resulting in dose modification occurred in 27%, and an adverse reaction resulting in treatment interruption occurred in 23%. The most common hematologic adverse reactions (incidence > 35%) are anaemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence > 20%) are infections (eitherogen not specified) and viral infection. Table 7 presents the most frequent non-laboratory adverse reactions occurring up to Cycle 7 Day 1 of randomized treatment.

### Table 7: Chronic Graft-versus-host Disease: All-grade ≥ 10% and Grades 3-5 (≥ 3%) Non-laboratory Adverse Reactions Occurring in Patients in the Open-label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=115)</th>
<th>Best Available Therapy (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Edema</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

### Table 8: Chronic Graft-versus-host Disease: Selected Laboratory Abnormalities in the Open-label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=165)</th>
<th>Best Available Therapy (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

* Presented values are worst Grade values regardless of baseline
* National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Clinically relevant laboratory abnormalities are shown in Table 4.

### Table 4: Polychnemia Vera: Selected Laboratory Abnormalities in the Open-label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Hypertiglyceridemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

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

### Table 6: Acute Graft-versus-host Disease: Selected Laboratory Abnormalities Worsening from the Baseline in the Open-label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Hypertiglyceridemia</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

* Grouped terms that are composites of applicable adverse reaction terms.

Clinically relevant laboratory abnormalities are shown in Table 8.

### Table 8: Chronic Graft-versus-host Disease: Selected Laboratory Abnormalities in the Open-label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=165)</th>
<th>Best Available Therapy (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
<tr>
<td>Hypertiglyceridemia</td>
<td>Grade 3 1%</td>
<td>Grade 3 1%</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
and effectiveness of Jakafi for treatment of pediatric patients have not been established. The safety and efficacy of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients younger than 12 years old. The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents [see Clinical Studies (14.3, 14.4) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. 

Lactation: 

Ruxolitinib and/or its metabolites were present in the milk of lactating women at doses of less than or equal to 200 mg daily. Ruxolitinib was initiated earlier in the postnatal period. These effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. Geriatric Use: 

The safety and effectiveness of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients have not been established. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults [see Clinical Studies (14.3) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. 

Hepatic Impairment: 

Exposure of ruxolitinib increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. [see Clinical Pharmacology (12.3) in Full Prescribing Information]. 

OVERDOSAGE: 

There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Hemodialysis is not expected to enhance the elimination of Jakafi.
McKay Discusses Important Updates in Treatment, Management of Clear Cell RCC

CASE

- A Black woman, aged 59 years, received a diagnosis of clear cell renal cell carcinoma (ccRCC).
- She underwent left total nephrectomy in December 2019.
- Nine months later, she developed metastatic disease to bilateral lung, mediastinum (35 × 38 mm), and retroperitoneal lymph nodes.
- Diagnosis: stage IV RCC, clear cell histology, with metastases to lung and retroperitoneum
- Karnofsky performance status: 90%
- Hemoglobin: 11.1 g/dL
- Corrected calcium, neutrophils, platelets within normal limits
- The patient received pembrolizumab plus lenvatinib as part of a clinical trial.

Rana R. McKay, MD
Associate Professor of Medicine
UC San Diego Health
Medical Oncologist
Koman Family Outpatient Pavilion
La Jolla, CA

Targeted Oncology™: Can you discuss the most recent updates in the guidelines for treating ccRCC?

McKay: The most recent version of the National Comprehensive Cancer Network (NCCN) guidelines are from June of this year.1 We are trying to be better on the guidelines panel with breaking up the preferred regimens based on level 1 and phase 3 data.

For favorable-risk patients, preferred regimens include the IO [immunotherapy]/TKI [tyrosine kinase inhibitor] combinations, whether that be axitinib [Inlyta]/pembrolizumab [Keytruda], cabozantinib [Cabometyx]/nivolumab [Opdivo], or lenvatinib [Lenvima]/pembrolizumab. For the poor-[risk] and intermediate-risk patients, we have all the above options, with the addition of nivolumab plus ipilimumab [Yervoy], and the addition of cabozantinib, based on data from the CABOSUN trial [NCT01835158],2 for those patients who may not necessarily be candidates for IO therapy.

The other regimens under column 2 of the NCCN guidelines for favorable risk also include nivolumab/ipilimumab, so it’s not necessarily excluded from use in the favorable-risk patients but it’s not under the preferred regimens. Under some circumstances, active surveillance could certainly be an option for those favorable-risk individuals.

I feel with every passing meeting we need to keep updating information for immune checkpoint inhibitor combination trials [for patients with metastatic RCC]. For instance, CheckMate 9ER [NCT03141177] now has the largest population of patients who had poor-risk disease [compared with other trials].3 The JAVELIN Renal 101 trial [NCT02684006]4 is not [discussed as much], because that trial has not read out for overall survival [OS] yet. Even though it’s an FDA-approved regimen, I think in clinical practice that regimen’s not being used.

The CLEAR study [NCT02811861] included the least number of patients with poor-risk disease and the KEYNOTE-426 [NCT02853331] trial enrolled the highest proportion of patients who had favorable-risk disease.5-11 The median follow-up was 67.7 months in the CheckMate 214 trial [NCT02231749] that had the longest follow-up [and a median OS of 47 months (95% CI, 35.4-57.4) on nivolumab plus ipilimumab vs 26.6 months (95% CI, 22.1-33.5) for patients on sunitinib ([Sutent] HR, 0.68; 95% CI, 0.58-0.81, P < .0001)].12,13 We’ve also got almost 4 years of follow-up from KEYNOTE-426 and then about 32 to 33 months from CheckMate 9ER and CLEAR, respectively.

All these regimens did demonstrate statistically significant improvement in OS, and the HR held steady right around 0.72 across these trials in the intent-to-treat populations. It is also important to look at the landmark OS at 12 months and 24 months that ideally, we would even have 36 months here, but we just don’t have that follow-up for the later studies.

Clearly, there are statistically significant improvements in OS across these data, and it is the durability that’s so impressive—that even at 30 months and after, we’re seeing that 70% hold steady over time, which I think is reassuring, providing the durability of nivolumab. For other trials there just isn’t as much follow-up yet, but hopefully we’ll continue to monitor the rates of patients who
As you’re thinking about regimens to use, if you’ve got a patient who needs an immediate response to treatment [and] you need to get their disease controlled, you can’t afford to have them have a PD as best response.”

—RANA R. MCKAY, MD

continue to be disease controlled without progression at 3, 4, 5 years out from treatment initiation.

I think the [progression-free survival] PFS data are superior, and I think the IO/TKI regimens induce a response quicker. The response rates are higher with those regimens, as compared with CheckMate 214 with nivolumab/ipilimumab. Then, as we look at complete response [CR] rates, I think these vary upward to 12% with CheckMate 214 [and] 16%, which is the highest, with the CLEAR trial, but keep in mind that this trial included the least number of patients with poor-risk disease and many patients who had favorable-risk disease, so it’s hard to totally compare.

The primary progressive disease [PD] rate is about 1 in 5 for CheckMate 214 with nivolumab/ipilimumab. The rates of primary PD with CheckMate 9ER and with CLEAR from nivolumab plus cabozantinib and lenvatinib plus pembrolizumab are less than 10%.

As you’re thinking about regimens to use, if you’ve got a patient who needs an immediate response to treatment [and] you need to get their disease controlled, you can’t afford to have them have a PD as best response. The nivolumab plus cabozantinib and lenvatinib plus pembrolizumab may be good regimens to use in that context, but for somebody [for whom] you’re worried about that almost-1-in-5 PD rate, that’s something to consider with the nivolumab/ipilimumab data.

**What is the CR rate for high-dose IL-2?**

The CR rate with high-dose IL-2 is less than 10%. When we used to select patients for high-dose IL-2, it was patients in the favorable-risk category as opposed to individuals in the intermediate[-risk] or poor-risk [categories]. If we think of high-dose IL-2, it’s somebody who had prior nephrectomy and they’re presenting with low-volume disease and perfect health; that was your optimal candidate for high-dose IL-2.

There could be a role for high-dose IL-2, but it’s been largely supplanted with the nivolumab/ipilimumab data, given the durability of the response. Durability of response is at 30% for nivolumab/ipilimumab, where you’re likely “curing” patients at the 30% mark—just under [one-]third of patients, but again, the primary PD rate is 1 in 5, and then everybody’s sort of in the middle.

**Are there any ideal biomarkers you are excited about in this setting?**

The most exciting thing right now is probably the RNA signatures. The IMmotion151 trial [NCT02420821] looked at atezolizumab [Tecentriq] plus bevacizumab [Avastin] vs sunitinib in the frontline setting, and although that trial was ultimately a negative study, there was some rich correlative work done doing [RNA sequencing] on the baseline biopsies, archival nephrectomy specimens, and clustering patients into 6 to 7 categories.

There are also signatures that seem associated with response to VEGF inhibition, whereas other signatures seem associated with response to IO. Thinking of a rational way to design a trial where you stratify therapy based on the signature is being explored now, but I think there’s no front-runner in the clinic, and PD-L1 status has not been very helpful with treatment selection for RCC.

**Do you ever look at circulating tumor DNA magnitude decrease to look to counteract pseudoprogression?**

Circulating tumor cells [CTCs] have been another challenging area in RCC because, unlike other solid tumor malignancies such as prostate cancer and breast cancer, which use epithelial cell adhesion molecule [EpCAM] capture to identify CTCs, RCC does not express EpCAM. The detection mechanism is different in RCC.

There are many research labs working on different captures, whether it be through CA9 and CA12 or the cytokeratins to try to identify the RCCs in circulation. I think Epic has a platform where they’re basing it solely off morphology, but I think CTC capture has been more difficult in RCC, and that classic CTC conversion that we see in prostate cancer, going from greater than 5 to less than 5, has not necessarily been validated in RCC treatment.
Can you highlight the results of the CLEAR trial? This was a phase 3 trial that looked at frontline lenvatinib plus pembrolizumab, or lenvatinib plus everolimus [Afinitor], vs sunitinib. The patients who were enrolled in the trial were patients with ccRCC who were treatment naive with a Karnofsky performance status of 70 or higher. The patients had measurable disease; stratification factors were largely based on a region of the world where the patients were enrolled, and Memorial Sloan Kettering Cancer Center [MSKCC] risk stratification.

This was one of the only frontline trials to date that had 3 arms to which patients were getting randomized. The primary end point was PFS by independent review, based on RECIST, and secondary end points included survival, objective response, safety, and health-related quality of life.

Something key is the dosing of the lenvatinib. In the combination with pembrolizumab, the lenvatinib dose is at 20 mg, and in the combination with everolimus, lenvatinib dose is at 18 mg.

We don’t use monotherapy lenvatinib in RCC, but monotherapy dosing is at 24 mg. With the lenvatinib dose, the strategy on this trial has been to start high and down-titrate, as opposed to CheckMate 9ER where there was a more middle-of-the-road dose selected, but the dose of lenvatinib here was 20 mg in combination with pembrolizumab.

At a median follow-up of 26.6 months, the combination of lenvatinib plus pembrolizumab resulted in a statistically significant improvement in PFS over sunitinib, with HR of 0.39 [95% CI, 0.32-0.49; P < .001]. The median PFS for lenvatinib/pembrolizumab was at 23.9 months [95% CI, 20.8-27.7]—that’s the longest PFS we’ve seen across all the 4 trials. Additionally, the combination of lenvatinib plus everolimus did demonstrate a statistically significant

### Table: PFS by Subgroup in Updated CLEAR Study Data

<table>
<thead>
<tr>
<th>SUBGROUP</th>
<th>PFS EVENTS/PATIENTS</th>
<th>HR (95% CI)</th>
<th>MEDIAN PFS, MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L + P</td>
<td>S</td>
<td>L + P vs S</td>
</tr>
<tr>
<td>Baseline bone metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39/85</td>
<td>54/97</td>
<td>0.33 (0.21-0.52)</td>
</tr>
<tr>
<td>No</td>
<td>121/270</td>
<td>151/260</td>
<td>0.42 (0.33-0.54)</td>
</tr>
<tr>
<td>Baseline liver metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34/60</td>
<td>35/61</td>
<td>0.43 (0.25-0.75)</td>
</tr>
<tr>
<td>No</td>
<td>126/295</td>
<td>170/296</td>
<td>0.37 (0.29-0.47)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS &gt; 1</td>
<td>51/107</td>
<td>78/119</td>
<td>0.40 (0.27-0.58)</td>
</tr>
<tr>
<td>CPS &lt; 1</td>
<td>48/112</td>
<td>58/103</td>
<td>0.39 (0.26-0.59)</td>
</tr>
<tr>
<td>NA</td>
<td>61/136</td>
<td>69/135</td>
<td>0.42 (0.29-0.60)</td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107/262</td>
<td>163/275</td>
<td>0.37 (0.28-0.47)</td>
</tr>
<tr>
<td>No</td>
<td>53/93</td>
<td>42/82</td>
<td>0.44 (0.28-0.68)</td>
</tr>
<tr>
<td>Sarcomatoid component by histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19/28</td>
<td>16/21</td>
<td>0.39 (0.18-0.84)</td>
</tr>
<tr>
<td>No</td>
<td>141/327</td>
<td>189/336</td>
<td>0.38 (0.31-0.48)</td>
</tr>
</tbody>
</table>

CPS, combined positive score; L, lenvatinib; P, pembrolizumab; PFS, progression-free survival; S, sunitinib; NA, not available.
improvement in PFS over sunitinib, with HR here of 0.65 [95% CI, 0.53-0.80; \( P < .001 \)].

The lenvatinib/everolimus arm had a PFS of 14.7 months [95% CI, 11.1-16.7]. With regard to the sunitinib arm here, probably a little bit better than what we would see at 9.2 months [95% CI, 6.0-11.0], but that was the performance of the control arm. Broken down by subgroups, including MSKCC risk group for those patients with favorable-[risk], intermediate-[risk], and poor-risk disease, there was a favoring of lenvatinib/pembrolizumab over sunitinib, with the direction of the HR being less than 1 across the different subgroups.

Updated subgroups, published in an abstract from the European Society of Oncology Meeting [2022]—including patients with the presence of baseline bone metastases, baseline liver metastases, PD-L1 status identified by their combined positive score, prior nephrectomy status, and the presence or absence of sarcomatoid histology—also saw a PFS benefit with lenvatinib and pembrolizumab over sunitinib [Table 19].

[Looking at the] OS data at a median follow-up of 26.6 months, we see a statistically significant improvement in OS, with lenvatinib plus pembrolizumab vs sunitinib.\(^7,9\) The HR here is 0.66; that was also statistically significant [95% CI, 0.49-0.88; \( P = .005 \)]. However, the median is not yet reached across all these groups. When we look at the combination of lenvatinib/everolimus vs sunitinib, this was not different than the sunitinib-treated patients. The HR here was 1.15, and the HRs did cross 1. The \( P \) value here was not significant, so there was no improvement in OS with frontline lenvatinib/everolimus, but we did demonstrate that with lenvatinib/pembrolizumab.

Updated data had a 33.7-month follow-up that showed the HR still demonstrated improvement over sunitinib but did drift upward a bit to 0.72 [95% CI, 0.55-0.93] from the initial reporting out of 0.66.\(^7,9\) The objective response rate [ORR] is the highest we’ve seen with this combination [lenvatinib/pembrolizumab] at 71%, 53.5% with lenvatinib/everolimus, and 36.1% with sunitinib.\(^7,8\) Again, the lenvatinib/pembrolizumab CR rate was at 16.1%, a primary PD rate of 5.4%. These are things to think about as you’re selecting regimens. Among patients who experienced a CR with lenvatinib plus pembrolizumab, at 24 months, 79% of patients maintained a CR, and at 36 months 74% of patients maintained a CR.

**What was the safety profile observed in this study?**

One thing to highlight is the grade 3 or higher adverse events [AEs], which with lenvatinib plus pembrolizumab was seen in 82.4% [of patients], 83.1% with lenvatinib/everolimus, and 71.8% with sunitinib but with high rates of grade 3 toxicity.\(^7\) The AEs that resulted in dose reduction or dose modification were seen in 68.8% of patients treated with lenvatinib plus pembrolizumab.

The proportion of patients who needed to discontinue both drugs of the regimen, meaning permanently discontinue the whole regimen, was at 13.4%. Some AEs, like hepatotoxicity, were not at a frequency of greater than 20% of the population. The biggest AEs to keep in mind are diarrhea; the hypertension is key and stands out; the proteinuria is key, stands out; hand-foot syndrome [palmar-plantar erythrodysesthesia].

**Can you discuss the dosing strategy for lenvatinib/pembrolizumab?**

The recommended dosage for lenvatinib is 20 mg daily, with the pembrolizumab at 200 mg every 3 weeks, and that’s basically continued until disease progression or for up to 2 years. After completion of 2 years of combination therapy, lenvatinib can be administered as a single agent until PD. That’s how the trial was designed: that at the 2-year mark, based on investigator assessment, the pembrolizumab could be discontinued. The dosing strategy [of this treatment is] 20 mg, 14 mg, 10 mg, and 8 mg daily, and then, based on toxicity, whether it be persistent grade 2 or grade 3 toxicity, dose reducing as needed.

**What are the highlights of the CheckMate 9ER data, and how has the trial influenced treatment management?**

This study looked at nivolumab plus cabozantinib.\(^3,5,6\) This was for patients with ccRCC, any IMDC [International Metastatic RCC Database Consortium] risk, randomized to receive cabozantinib at 40 mg plus nivolumab. The nivolumab was given on [an every-2-week] schedule—and certainly it can be given on [an every-4-week] schedule—vs sunitinib.

[The primary end point was also PFS and] at the median follow-up of 18.1 months, showing a statistically significant improvement in PFS at 16.6 months vs 8.3 months, with HR of 0.51 [95% CI, 0.41-0.64; \( P < .001 \)].\(^5\) Updated data from the 2021 American Society of Clinical Oncology Genitourinary Cancers Symposium at the 33-month median follow-up: the median PFS is at 16.6 months for the combination arm vs 8.3 months for the sunitinib arm with the HR holding steady at 0.56 [95% CI, 0.46-0.68].\(^16\)

**Were there any subgroups in this trial worth noting?**

[There was a] subgroup analysis for PFS, looking at the region [patients were from]; IMDC risk including...
favorable, intermediate, and poor; PD-L1 status; age; gender; performance status; presence of bone metastases; and whether patients had a nephrectomy.5,6 Across all subgroups, PFS was favoring treatment with nivolumab/cabozantinib.

At the 33-month median follow-up, the median OS was at 37.7 months for the combination vs 34.3 months for sunitinib, with HR of 0.70 [95% CI, 0.55-0.90], and the 12-month landmark OS rate is at 70.3% compared with 60.3%, respectively.

The CR rate here was at 8% with a primary PD rate at 5.6%.3 The ORR is at almost 56% with the combination [95% CI, 50.1%-61.2%]. At the 33-month follow-up, the CR rate did increase from 8.0% initially to 12.4%. Some of these PRs converted into CRs with longer follow-up, and then the ORR holding steady at 55.7%.

The big point to highlight with AEs in this regimen is the rates of treatment discontinuation. The rates of somebody needing to discontinue either regimen at the initial data cutoff here was at 6.1%—very low rate of needing to discontinue this regimen, unlike the data we just saw. Treatment-related AE discontinuation rate at the 23.5-month follow-up for the [combination]—this was updated—was at 6.6%. That’s important, and the treatment-related AEs for grade 3 or higher at 65%, compared with 54% with sunitinib.

The major grade 3 or greater AEs to watch out for [from this study were] diarrhea [n = 6], hand-foot syndrome [n = 8], and hypertension [n = 11]. The grade 3 events are about on par with sunitinib; it’s just that there’s more grade 1/2 diarrhea, which is the big one [overall], and [aspartate aminotransferase] AST/ALT [alanine aminotransferase] elevation is something to keep considering.

REFERENCES

## INDICATION
LENVIMA® is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

### IMPORTANT SAFETY INFORMATION

#### Warnings and Precautions

**Hypertension.** In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3). In HCC (renal cell carcinoma), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week; then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

**Cardiac Dysfunction.** Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Arterial Thromboembolic Events.** Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

**Hepatotoxicity.** Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients. 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Renal Failure or Impairment.** Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

### Statistical superiority vs sorafenib in select secondary efficacy endpoints, PFS and ORR, according to mRECIST†

**Nearly 3.5X ORR, 41% with LENVIMA vs 12% with sorafenib†**

<table>
<thead>
<tr>
<th>Event</th>
<th>LENVIMA</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response: 21% (n=10) with LENVIMA vs 0.8% (n=4) with sorafenib</td>
<td>Complete response: 0.4% (n=2) with LENVIMA vs 0.2% (n=1)</td>
<td></td>
</tr>
<tr>
<td>Partial response: 38.5% (n=184) with LENVIMA vs 11.6% (n=55) with sorafenib</td>
<td>Partial response: 18.4% (n=88) with LENVIMA vs 6.3% (n=30)</td>
<td></td>
</tr>
</tbody>
</table>

*Based on an masked independent imaging review according to mRECIST.†

**REFLECT:**** in a large (N=954), phase 3, multicenter, randomized, open-label trial in patients with previously untreated unresectable HCC vs sorafenib, LENVIMA met the primary endpoint.**

13.6-month median OS, proven noninferior to sorafenib (12.3 months)

- **HR: 0.92 (95% CI: 0.79-1.06)***
- **Number of events: 351 (73%) with LENVIMA and 350 (74%) with sorafenib**
- **LENVIMA did not demonstrate a statistically significant improvement in OS vs sorafenib†**

*Based on stratified Cox-model. The noninferiority margin for the HR of LENVIMA vs sorafenib is 1.08.†
Double the median PFS achieved with LENVIMA vs sorafenib\(^1,3\)

Statistically superior PFS (mRECIST) per independent radiology review

![Graph showing PFS comparison between LENVIMA and sorafenib](image)

**Number of subjects at risk**

<table>
<thead>
<tr>
<th>LENVIMA</th>
<th>sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>478</td>
<td>476</td>
</tr>
</tbody>
</table>

**Number of events**

<table>
<thead>
<tr>
<th></th>
<th>LENVIMA</th>
<th>sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>351</td>
<td>323</td>
<td></td>
</tr>
</tbody>
</table>

An independent assessment using RECIST 1.1 criteria demonstrated a median PFS of 7.3 months with LENVIMA vs 3.6 months with sorafenib (HR: 0.65 [95% CI 0.56-0.77])\(^1\)

**Adverse reaction profile\(^1\)**

The most common adverse reactions observed in LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.

HCC=hepatocellular carcinoma; REFLECT=A Multicenter, Randomized, Open-label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma; OS=overall survival; HR=hazard ratio; CI=confidence interval; PFS=progression-free survival; ORR=objective response rate; mRECIST=modified Response Evaluation Criteria; RECIST=Response Evaluation Criteria in Solid Tumors.

In REFLECT, patients enrolled had Child-Pugh A and BCLC Stage C or B HCC and were ineligible for local liver-directed therapy, had an ECOG PS of 0 or 1, had received no prior systemic therapy for HCC, and had ≥1 measurable target lesion according to mRECIST for HCC. Patients were randomized (1:1) to receive LENVIMA (12 mg for baseline body weight <60 kg) orally once daily or sorafenib 400 mg orally twice daily until radiological disease progression or unacceptable toxicity. The primary endpoint was OS. REFLECT was designed to show the noninferiority of LENVIMA to sorafenib for OS. Select secondary efficacy endpoints were PFS and ORR according to mRECIST for HCC.

**Important Safety Information**

**Warnings and Precautions (cont’d)**

**Proteinuria.** In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. withheld and resumed at reduced dose upon recovery or permanently discontinue based on severity.

**Diarrhea.** Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus-treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea occurred despite dose reduction. Promptly initiate management of diarrhea. withheld and resumed at reduced dose upon recovery or permanently discontinue based on severity.

**Fistula Formation and Gastrointestinal Perforation.** Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

**QT Interval Prolongation.** In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class la and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

**Hypocalcemia.** In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 86% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information.

Visit www.LENVIMA.com/hcp to learn more
IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont’d)

Hypocalcemia (cont’d). Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal intracranial hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week 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 LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Adverse Reactions

In RCC, the most common adverse reactions (≥20%) observed in LENVIMA-treated patients were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), decreased weight (31%), abdominal pain (30%), palmar-planter erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%), hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%). The most common serious adverse reactions (≥2%) were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reductions or interruption in 62% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were fatigue (9%), ≥grade 1 or 2 hypothyroidism (21%), and nausea (20%). In RCC and HCC, grade 3 or 4 fistula occurred in 1.4% of patients. In RCC, grade 3 or 4 gastrointestinal fistulas occurred in 1.4% of patients. In RCC, QT interval prolongation of >500 ms occurred in 2% of patients. In RCC, QTc interval >500 ms occurred in 2% of patients.

In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (renal cell carcinoma (SELECT)), the median time to onset of new or worsening hypertension was 4 weeks. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypokinesia, or decrease in left or right ventricular ejection fraction) occurred in 799 patients with DTC, RCC or HCC, Grade 3 or higher cardiac dysfunction occurred in 29% of LENVIMA-treated patients and 21% of sorafenib-treated patients; 2% of patients discontinued LENVIMA and 0.2% discontinued sorafenib due to cardiac dysfunction.

Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose if cardiac dysfunction persists despite dose reduction.

Hepatotoxicity

Of 799 patients treated with LENVIMA or sorafenib in SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 16% of patients treated with LENVIMA and 28% of patients treated with sorafenib. Grade 3 or 4 proteinuria occurred in 2% of patients treated with LENVIMA and 6% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 8% of patients treated with LENVIMA and 14% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib.

Select (DTC), Study 205 (RCC) and REFLECT (HCC), hemorrhagic events of any grade occurred in 29% of patients treated with LENVIMA and 47% of patients treated with sorafenib. Grade 3 or 4 hemorrhagic events occurred in 3% of patients treated with LENVIMA and 9% of patients treated with sorafenib. Grade 3 or higher hemorrhagic events occurred in 2% of patients treated with LENVIMA and 6% of patients treated with sorafenib. Grade 3 or higher hemorrhagic events occurred in 2% of patients treated with LENVIMA and 6% of patients treated with sorafenib.

Select (DTC), Study 205 (RCC) and REFLECT (HCC), grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 16% of patients treated with LENVIMA and 28% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 8% of patients treated with LENVIMA and 14% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib.

Select (DTC), Study 205 (RCC) and REFLECT (HCC), grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 16% of patients treated with LENVIMA and 28% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 8% of patients treated with LENVIMA and 14% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib.

Select (DTC), Study 205 (RCC) and REFLECT (HCC), grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 16% of patients treated with LENVIMA and 28% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 8% of patients treated with LENVIMA and 14% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib. Grade 3 or higher proteinuria ≥2 g or greater proteinuria per 24 hours occurred in 2% of patients treated with LENVIMA and 5% of patients treated with sorafenib.
Avoid invasive dental procedures, if possible, while on LENVIMA treatment, to maintain good hygiene practices and to consider having preventive dentistry performed. Bisphosphonates, denosumab, dental disease, or invasive dental procedures in patients with extremely impaired wound healing should be avoided.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modifications for LENVIMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Grade 3</td>
<td>Withhold for Grade 3 that persists despite antihypertensive therapy.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Cardiac Dysfunction</td>
<td>Grade 3</td>
<td>Withhold until improves to Grade 0 or 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Arterial Thromboembolic Event</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Grade 3 or 4</td>
<td>Withhold until improves to Grade 0 or 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue for hepatic failure.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 g or greater proteinuria in 24 hours</td>
<td>Withhold until less than or equal to 2 g of proteinuria per 24 hours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue for nephrotic syndrome.</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Fistula Formation</td>
<td>Grade 3 or 4</td>
<td>Withhold until fully resolved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of necrotizing lesion.</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Greater than 500 ms or greater than 60 ms increase from baseline</td>
<td>Withhold until improves to less than or equal to 480 ms or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td>Reversible Posterior Leukoencephalopathy Syndrome</td>
<td>Any Grade</td>
<td>Withhold until fully resolved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of necrotizing lesion.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Persistent or intermittent Grade 2 or 3 adverse reaction</td>
<td>Withhold until improves to Grade 0 or 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 laboratory abnormality</td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 adverse reaction</td>
<td>Permanently discontinue.</td>
</tr>
</tbody>
</table>

Table 2. Recommended Dosage Reductions of LENVIMA for Adverse Reactions

<table>
<thead>
<tr>
<th>Indication</th>
<th>First Dosage Reduction To</th>
<th>Second Dosage Reduction To</th>
<th>Third Dosage Reduction To</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Actual weight 60 kg or greater</td>
<td>8 mg once daily</td>
<td>4 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Actual weight less than 60 kg</td>
<td>4 mg once daily</td>
<td>4 mg every other day</td>
</tr>
</tbody>
</table>

Preparation and Administration LENVIMA capsules can be swallowed whole or divided in a small amount of liquid. To dissolve in liquid, pour the capsule contents in a tablespoon of water or apple juice without breaking or crushing the capsule. Leave the capsules in the water or apple juice for at least 10 minutes. Stir for at least 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swallow the contents a few times and swallow the water or apple juice.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS

Hypertension Hypertension occurred in 73% of patients in SELECT (differentiated thyroid cancer or DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 28 days in SELECT and 28 days in REFLECT. Grade 1 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 2 or higher hypertension occurred in 19% of patients in SELECT and 8% in REFLECT. In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (renal cell carcinoma or RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 hypertension occurred in 8% of patients in Study 205. Systolic blood pressure >170 mmHg occurred in 29% of patients and diastolic blood pressure >100 mmHg occurred in 21%.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiating LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 4 months, and then at least monthly thereafter during treatment. Withhold and restart at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity.

Cardiac Dysfunction Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in SELECT (DTC), Study 205 (RCC), HCC, or RCC with uncontrolled RCC, Grade 3 or higher cardiac dysfunction occurred in 10% of patients (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypertrophy, or death). A left or right ventricular ejection fraction of <20% from baseline occurred in 3% of LENVIMA-treated patients. Monitor and manage patients for clinical symptoms of cardiac dysfunction. Withhold and restart at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity.

Arterial Thromboembolic Events Among patients receiving LENVIMA or LENVIMA with everolimus, arterial thromboembolic events of any severity occurred in 7% of patients receiving LENVIMA in SELECT (DTC) and 5% of patients receiving LENVIMA in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Hepatotoxicity Among clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than RCC, serious hepatic adverse reactions occurred in 14% of patients, fatal events, including hepatic failure, occurred in 0.4% of patients.

In REFLECT (HCC), hepatic encephalopathy (including hepatic encephalopathy, encephalopathy, metabolic encephalopathy, and hepatic coma) occurred in 8% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Grade 3 to 4 hepatic encephalopathy occurred in 15% of patients receiving LENVIMA, 15% of patients receiving sorafenib, and 7% of patients receiving placebo. Grade 3 to 4 hepatic failure occurred in 3% of LENVIMA-treated patients and 3% of sorafenib-treated patients. 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% of patients discontinued lenvatinib or sorafenib due to hepatic failure.

Monitor liver function prior to initiating LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with known liver disease and drug-induced liver injury for signs and symptoms of hepatic dysfunction. Withhold and restart at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Renal Failure or Impairment Serious but not fatal renal failure or impairment can occur with LENVIMA.

Renal impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients receiving LENVIMA in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatal event in each study.

In Study 206 (RCC), renal impairment or renal failure occurred in 18% of patients receiving LENVIMA with everolimus, including Grade 3 in 10% of patients.

Initiate prompt management of diuretics or dehydration/hypovolemia. Withhold and restart at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Proteinuria Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of LENVIMA-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (HCC), proteinuria occurred in 31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus.

Monitor for proteinuria prior to initiating LENVIMA and periodically during treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24-hour urine protein. Withhold and restart at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Diarrhea Diarrhea was the second most common adverse event in patients treated with LENVIMA as a single agent or in combination with everolimus. Diarrhea occurred in 69% of patients treated with LENVIMA as a single agent or in combination with everolimus.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrolyte abnormalities and correct any abnormalities prior to initiating treatment. Withhold and restart at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Fistula Formation and Gastrointestinal Perforation Of 799 patients treated with LENVIMA or LENVIMA with everolimus in SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), fistula or gastrointestinal perforation occurred in 2%.

Permanently discontinue LENVIMA in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula.

GT Interval Prolongation In SELECT (DTC), GT interval prolongation occurred in 9% of LENVIMA-treated patients and GT interval prolongation of >500 ms occurred in 2%. In Study 205 (HCC), QT interval increases of >500 ms occurred in 11% of patients receiving LENVIMA with everolimus and QTc interval >500 ms occurred in 6%. In REFLECT (HCC), QT interval increases of >500 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrolyte abnormalities and correct any abnormalities prior to initiating treatment. Withhold and restart at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Hepatocellular Carcinoma Patients who received LENVIMA as a single agent, reversible posterior leukoencephalopathy syndrome (RPLS) occurred in 0.3%.

Confirm the diagnosis of RPLS with magnetic resonance imaging. Withhold and restart at a reduced dose upon recovery or permanently discontinue LENVIMA depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events Serious but fatal hemorrhagic events can occur with LENVIMA. Across SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), hemorrhagic events of any grade occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria.
Cardiac Dysfunction
effective contraception during treatment with LENVIMA and for at least 30 days after the last dose. Oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses is contraindicated. Based on its mechanism of action and data from animal reproduction studies, LENVIMA should be avoided in women of reproductive potential. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk of developing ONJ. ONJ has been reported in patients receiving LENVIMA. Concomitant procedures, may increase the risk of ONJ. Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing
Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk of developing ONJ. ONJ has been reported in patients receiving LENVIMA. Concomitant procedures, may increase the risk of ONJ. Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Osteonecrosis of the Jaw (ONJ)
permanently discontinue LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity
Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk of developing ONJ. ONJ has been reported in patients receiving LENVIMA. Concomitant procedures, may increase the risk of ONJ. Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles (e.g. carotid artery). Withhold and resume at reduced dose and safety or permanently discontinue LENVIMA based on the severity.

Vascular
Hypertension

Diabetes

Hypothyroidism according to standard medical practice.

Avastin, bevacizumab, and erlotinib resulted in substantially higher rates of severe hypertension when added to LENVIMA.

Hematology

Hepatocellular Carcinoma
Hepatobiliary:

Gastrointestinal:

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the Warnings and Precautions reflect exposure to LENVIMA as a single agent in 261 patients with hepatocellular carcinoma (HCC) (SELECT) and 476 patients with RCC (REFLECT). LENVIMA was administered in 428 patients with endometrial carcinoma (Study 309). LENVIMA with everolimus in 62 patients with RCC (Study 202), and LENVIMA with pembrolizumab in 382 patients with RCC (CLEAR). Safety data obtained in 1823 patients with hepatocellular carcinoma, renal cell carcinoma and uterine cervical carcinoma were used to further characterize the risk of serious adverse reactions. Among the 1823 patients who received LENVIMA as a single agent, the median age was 61 years (20 to 89 years), the dose range was 0.2 mg to 32 mg daily, and the median duration of exposure was 5.6 months. The data below reflect exposure to LENVIMA in 1597 patients enrolled in randomized, active-controlled trials (REFLECT, Study 205; CLEAR, Study 309), and a randomized, placebo-controlled trial (SELECT). The median duration of exposure to LENVIMA across these five studies ranged from 6 to 18 months. The demographic and exposure data for each clinical trial population are described in the subsections below.

Hepatocellular Carcinoma
The safety of LENVIMA was evaluated in REFLECT, which randomized 1,111 patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=478) or sorafenib (n=541). The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight of ≥60 kg and 8 mg orally once daily for patients with a baseline body weight of <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was 16 months in 49% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 478 patients who received LENVIMA in REFLECT, the median age was 52 years, 85% were men, 9% were African Americans, and 38% were Asian. The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥2%) in patients receiving LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic vesicles, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA.
further characterize the risks of serious adverse reactions. Among the 1823 patients who received LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 3.

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated cohort, including hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

28% were White and 70% were Asian.

orally once daily for patients with a baseline body weight of ≥60 kg and 8 mg orally once daily for patients with a baseline body weight of <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment for patients with advanced renal cell carcinoma (RCC) and in 21% of patients receiving LENVIMA in REFLECT (HCC). In those patients with a normal or low 28% were White and 70% were Asian.

with a baseline body weight of <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment for patients with advanced renal cell carcinoma (RCC) and in 21% of patients receiving LENVIMA in REFLECT (HCC). In those patients with a normal or low

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman. Administration of LENVIMA to pregnant women may cause fetal harm and disrupt the milk transfer of LENVIMA.

• QT Interval Prolongation
• Cardiac Dysfunction
• Hypocalcemia
• Infertility

LENVIMA may impair fertility in males and females of reproductive potential

Verify the pregnancy status of females of reproductive potential prior to initiating LENVIMA.

Contraindication
Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman.

Adverse effects of LENVIMA were not dose-related in clinical trials.

Juvenile Animal Data
Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain), decreased food consumption, and decreases in the width and/or length of the femur and tibia and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 0.14 mg/kg (approximately 1.2 to 5 times the human exposure based on AUC at the recommended clinical dose of 24 mg).

Eisai/Lenvima

No dose adjustment is recommended for patients with mild (Ccr 60-89 mL/min) or moderate (Ccr 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe (Ccr 15-29 mL/min) renal impairment. Reduce the dose of lenvatinib for patients with RCC, DTC, or endometrial carcinoma and severe renal impairment. There is no recommended dose of LENVIMA for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease.

Hepatic Impairment No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC and moderate or severe hepatic impairment.

No dose adjustment is recommended for patients with DTC, RCC, or endometrial carcinoma and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C). Reduce the dose of lenvatinib for patients with RCC, DTC, or endometrial carcinoma and severe hepatic impairment.

OVERDOSAGE
Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multigorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.
Burger Details the Data to Help Choose Treatment in Chronic Lymphocytic Leukemia

CASE

- A woman, aged 71 years, reported weight loss and increasing fatigue.
- Medical history: hypertension, medically controlled
- Physical examination: axillary lymphadenopathy; spleen palpable about 4 cm below costal margin; appears ill and continues only limited daily activity
- Laboratory results:
  - White blood cell count: 47,000/µL; 76% lymphocytes
  - Hemoglobin: 8.7 g/dL
  - Platelet count: 115,000/µL
  - Lactate dehydrogenase: 250 U/L
  - \(\beta_2\)-Microglobulin: 4.3 mg/L
- Flow cytometry: CD5+, CD20+, CD23+, \(\kappa\)-restricted monoclonal B-cell population
- Fluorescence in situ hybridization: deletion 11q (del[11q])
- Molecular analysis: \(IGHV\) unmutated; TP53 unmutated
- Bone marrow biopsy: diffuse infiltration by chronic lymphocytic leukemia (CLL), 90%-95%

Jan A. Burger, MD, PhD
Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

Targeted Oncology™: What do the National Comprehensive Cancer Network (NCCN) guidelines recommend for a patient such as this?

BURGER: The most recent NCCN guidelines recommend the Bruton tyrosine kinase \([BTK]\) inhibitors acalabrutinib \([\text{Calquence}]\) with or without obinutuzumab \([\text{Gazyva}]\), ibrutinib \([\text{Imbruvica}]\), and venetoclax \([\text{Venclexta}]\) with or without obinutuzumab, \(\) all supported by category 1 data. Zanubrutinib \([\text{Brukinsa}]\) is listed also, but that is not FDA approved yet \([\text{for CLL}]\), but may be approved later this year or next.\(^1\)

The chemotherapeutic approaches, [once listed as “preferred regimens”], are now listed as “other recommended regimens.” That’s the result of many randomized studies that demonstrated better progression-free survival \([\text{PFS}]\) and, in some studies, better overall survival \([\text{OS}]\) with the new targeted agents, which are also better tolerated.

What data support the use of first-line ibrutinib for patients with CLL?

The study that put ibrutinib on the landscape was the phase 3 RESONATE-2 study \([\text{NCT01722487}]\), which started around 2012 or 2013. At that time, chlorambucil \([\text{Leukeran}]\) monotherapy was still considered a standard treatment, so patients were randomly assigned to receive either ibrutinib or chlorambucil. This study was for older patients, \([\text{at least age 65 years}]\), who had comorbidities.\(^2,3\)

We have followed these patients for 5 years or more, and we published and presented those data last year. There was a major difference in PFS from the beginning, favoring ibrutinib, but there was some decline \([\text{in PFS even in the experimental arm}]\), which I think was mostly driven by the development of adverse events \([\text{AEs}]\) rather than resistance to ibrutinib.

\([\text{Patients who develop AEs}]\) eventually must come off treatment and then progress. But the data clearly show that targeted therapy works much better than chlorambucil at median PFS for the experimental arm vs the comparator arm, that was not reached \([\text{NR}]\) vs 15 months, respectively \([\text{HR}, 0.160; 95\% \text{ CI}, 0.111-0.230]\).\(^4\) Similar studies like \([\text{iLLUMINATE (NCT02264574)}}\) and \(\text{ELEVATE-TN (NCT02475681)}\) have been done with chlorambucil plus obinutuzumab as a comparator arm, and the data looked quite similar.

When we talk about favorable vs unfavorable \([\text{status}]\), or high-[risk] vs low-risk \([\text{CLL}]\), those terms are helpful for predicting the time until the patient may require treatment. The treatment outcome for the formerly high-risk, \([\text{IGHV}-\text{unmutated patients (HR}, 0.109; 95\% \text{ CI}, 0.063-0.189)]\), was basically identical to that of the low-risk, \([\text{IGHV-mutated patients (HR}, 0.197; 95\% \text{ CI}, 0.096-0.394)]\). So, in terms of treatment outcome, the prognosis has much improved, and these high-risk patients have durable responses similar to those of their counterparts in the low-risk category at \([6.5\text{-year PFS, } 62\% \text{ vs } 67\%\), respectively].\(^5\)

\([\text{In contrast, the results for the chemotherapy arm were}]\) what we are used to: \([\text{IGHV}-\text{mutated patients fared better}]\)
than the [IGHV]-unmutated patients [6.5-year PFS rate, 18% vs 2%, respectively].

Five-year OS rate was not very different between the arms [83% in the experimental arm vs 68% in the comparator arm]. [Median OS was NR in both arms (HR, 0.514; 95% CI, 0.312-0.848)]. The difference in OS would be greater if there hadn’t been a crossover, but patients were allowed to cross over if they had disease progression after 12 months. That rescued some of these patients; obviously, if a patient progresses, you put them on other, [more] effective treatment.

What did the data reveal about the safety of this regimen?
There were not many serious AEs. In the experimental arm, there were some cases of pneumonia [4%] and some basal cell cancers [2.2%], which we often see in our patients with CLL. The AEs of clinical interest [included atrial fibrillation]; this was one of the first studies to point out that there is a risk for atrial fibrillation in patients who receive ibrutinib and less risk with chlorambucil. In this study, atrial fibrillation was observed in 6% vs 0.8% of the patients in the respective arms. That’s [approximately] 1 in 20 patients. That doesn’t necessarily mean the patients cannot continue treatment but obviously it is something you must make your patients aware of if you use BTK inhibitors, [especially] ibrutinib.

Hypertension was a more common cardiovascular AE, [affecting 14% of patients in the experimental arm vs 0% in the comparator arm]. There was also a slight risk of increased bleeding, [affecting 4% vs 2%, respectively]. All the BTK inhibitors have that effect because they affect platelet aggregation. If you have patients on anticoagulation therapy, you must watch them closely for bleeding events, especially when you initiate treatment, and you must hold treatment [if they] undergo any type of procedure where they could potentially bleed.

After 7 years, about half of the patients are still on treatment [47%], but some patients had to discontinue treatment, mostly because of AEs [23%]. Other patients [discontinued treatment because of] disease progression [12%] or for other reasons.

In this study, we are talking about older patients, so they were taking other medications. Additionally, many of the patients were on acid-reducing medications; more than half were on proton pump inhibitors [with 56% in the experimental arm vs 36% in the comparator arm, respectively]. These results tell you that you can safely [administer ibrutinib to] patients who are on these different medications if you monitor them carefully.

What data support the use of acalabrutinib as first-line treatment for CLL?
The phase 3 ELEVATE TN trial looked at acalabrutinib, the more recent, second-generation BTK inhibitor, which is a bit more selective for BTK. It inhibits [fewer] off-target kinases and the hope is that it therefore has a [less severe AE profile], and there are some data now to indicate that there are fewer cardiovascular AEs. This study was done in treatment-naive patients, divided among 3 arms: acalabrutinib plus obinutuzumab, single-agent acalabrutinib, and obinutuzumab plus chlorambucil.

PFS was best for patients in the acalabrutinib plus obinutuzumab arm. There was a slight PFS benefit from adding obinutuzumab to acalabrutinib, but not very much. [Median PFS was NR in both arms at a median follow-up of 46.9 months (HR, 0.56; 95% CI, 0.32-0.95; P=.0296)], and you have more AEs once you add obinutuzumab. The chlorambucil plus obinutuzumab arm was inferior, [with a median PFS of 27.8 months]. [For acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab, the HR was 0.10 (95% CI, 0.07-0.17; P<.0001)]. So, their conclusion was in favor of single-agent acalabrutinib, [which produced 78% PFS at 4 years]. Clearly, consistent with all the BTK inhibitor studies, this study had a very good outcome.

When the results were analyzed regarding mutation status, the survival curves were very similar; patients with unmutated IGHV and those with del(17p) or mutated TP53 were doing well [median PFS, NR], I think the message here is that the BTK inhibitors ibrutinib and acalabrutinib work very well in low-risk and high-risk patients.

OS looked very good [after a median follow-up of 46.9 months], even for the control arm, because patients could move on to a very effective treatment. [Median OS was NR for all arms; survival rates at 4 years was 93% in the acalabrutinib arm, 88% in the acalabrutinib arm, and 88% in the chlorambucil plus obinutuzumab arm].

What did the data reveal about the safety of this regimen?
In terms of safety, there’s not too much to point out. The most common AEs were [anemia, neutropenia, upper respiratory tract infection (URTI), thrombocytopenia, headache, musculoskeletal pain, and] diarrhea. The headaches are responsive to anything containing caffeine; they are usually not very severe and go away within the first couple of months. Overall, this is a very well-tolerated drug. Atrial fibrillation of any grade occurred [in 3.9%, 3.4%, and 0.6% of the patients in the acalabrutinib, acalabrutinib plus obinutuzumab, and chlorambucil plus obinutuzumab arms, respectively].

For hypertension, [the values were 4.5%, 7.3%, and 3.6%, respectively]. There were numerous bleeding events, [affecting 39.1%, 42.7%, and 11.8% of patients in the respective arms]; this was mostly bruising, as physicians will see in their ibrutinib-[treated] and acalabrutinib-treated patients. Some patients tend to bruise more easily, especially if so.
they aren’t on additional anticoagulation or antiplatelet agents. The occurrence of secondary malignancies, [which affected 2.8%, 5.6%, and 1.8% of patients in the respective arms], were probably just a result of patients being on long-term treatment and having some risk for other cancers.6,8

What data support first-line use of zanubrutinib?
Zanubrutinib, a new, second-generation BTK inhibitor, is not FDA-approved for CLL. It is approved for mantle cell lymphoma and for Waldenström macroglobulinemia.9,10 This drug was studied in the SEQUOIA trial [NCT03336333]. There were 3 cohorts in this trial; the data from cohort 1 reflect frontline treatment of CLL patients who received either zanubrutinib or bendamustine [Bendeka] plus rituximab [Rituxan]. The patient population was of a representative age, about 70 years, and [the patients did not have detectable del(17p)], so it was a very typical population of older frontline patients.11

PFS was analyzed and, as in [most of] the studies comparing BTK inhibitors to chemoimmunotherapy, there was a significant benefit from the new BTK inhibitor; [24-month PFS rate was 85.5% (95% CI, 80.1%-89.6%) vs 69.5% (95% CI, 62.4%-75.5%) for the experimental and comparator arms, respectively]. The IGHV-unmutated patients did better with zanubrutinib than with the comparator combination [HR, 0.24; 95% CI, 0.13-0.43; P<.001], [with results similar to those observed with ibrutinib].4,11 Additionally, the low-risk, mutated patients did OK with bendamustine plus rituximab [HR for zanubrutinib vs bendamustine plus rituximab, 0.67; 95% CI, 0.36-1.22; P=.186] and they certainly did better than the high-risk, [unmutated patients who received that combination].11 The overall response rate [ORR] was good. With the BTK inhibitors, you can’t expect to see a lot of complete remissions, but the ORR was high [94.6% (95% CI, 91.0%-97.1%) for the experimental arm vs 85.3% (95% CI, 80.1%-89.5%) for the comparator arm].11

It is exceedingly rare for a patient with CLL not to respond to a BTK inhibitor. If the patient does not respond, you must question your diagnosis [and consider whether] the patient may not have some other problem or maybe a different malignancy.

What did this study reveal about the safety profile of this drug?
Overall, zanubrutinib appeared to be a well-tolerated drug. There were some AEs in the zanubrutinib arm, but fewer than in the bendamustine plus rituximab arm; [AEs of grade 3 or higher affected 52.5% vs 79.7% of patients in the respective arms (Table 1)]. Dose reductions occurred sometimes, [in 7.5% vs 37.4% of the respective arms], although the follow-up was relatively short, [approximately 26 months].11 [The AEs that occurred most in this study are similar to what you’ve probably seen with other BTK inhibitors. These included arthralgia, [observed in 13.3% of patients in the experimental arm vs 8.8% of patients in the comparator arm]. In this study, among AEs of interest, there was certainly more myelotoxicity with the comparator than with zanubrutinib. There

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>ZANUBRUTINIB (n = 240)</th>
<th>BENDAMUSTINE + RITUXIMAB (n = 227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade all cause AEs</td>
<td>224 (93.3)</td>
<td>218 (96.0)</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>126 (52.5)</td>
<td>181 (79.7)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>88 (36.7)</td>
<td>113 (49.8)</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>11 (4.6)</td>
<td>11 (4.8)</td>
</tr>
<tr>
<td>AEs leading to dose reduction</td>
<td>18 (7.5)</td>
<td>84 (37.0)</td>
</tr>
<tr>
<td>AEs leading to dose interruption/delay</td>
<td>111 (46.3)</td>
<td>154 (67.8)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>20 (8.3)</td>
<td>31 (13.7)</td>
</tr>
</tbody>
</table>

AE, adverse event.
was a little bit of neutropenia in the zanubrutinib arm, affecting 15.8% of patients, which is not seen with acalabrutinib or ibrutinib. Dose reduction should fix that problem.

Atrial fibrillation was not very frequent, affecting only 3% of the patients in the experimental arm [vs 2.6% in the comparator arm], but that’s with a relatively short follow-up. Bleeding of any grade affected 45.0% [vs 11%, respectively], but major bleeding was not very frequent. There was some diarrhea [13.8% vs 13.7%, respectively] and some hypertension [14.2% vs 10.6%], but, overall, this was another well-tolerated drug.

REFERENCES
**Roundtable Discussion:**

Stinchcombe Reviews Second-Line Therapy for ES-SCLC

**CASE SUMMARY**

A 58-year-old, moderately active man presented with worsening shortness of breath, persistent dry cough, and fatigue. He was a smoker with a 30 pack-year history. He was given an ECOG performance score of 1. A chest x-ray showed opacity in the left lung and a chest CT scan showed a hilar mass, with invasion of the left pulmonary artery and 3 contralateral lung nodules present. A brain MRI was negative for metastases. After a bronchoscopy with transbronchial biopsy/pathology, he received a diagnosis of extensive-stage small cell lung cancer (ES-SCLC).

He received 4 cycles of carboplatin, etoposide, and atezolizumab (Tecentriq) and initially achieved a partial response. Seven months after his last cycle of platinum chemotherapy, shortness of breath returned with right upper quadrant pain and mid-back pain. A CT scan of the chest/abdomen/pelvis showed hematogenous metastases in the liver and adrenal glands, but imaging was negative for brain metastases. Laboratory results were within normal limits, and he still had an ECOG performance score of 1.

**DISCUSSION QUESTION**

How do you define platinum-sensitive vs platinum-resistant SCLC?

**MOHAMED:** Platinum-sensitive is if the recurrence occurs more than 6 months post treatment. Less than 3 months, or within 3 months, that's refractory. And 3 months to 6 months is a gray area where you can play around, but I would definitely consider 3 months to 6 months resistant, honestly, but 6 months definitely is sensitive.

**PATI:** Six months for platinum sensitive.

**RABARA:** I personally would use 6 months also.

**STINCHCOMBE:** How many of your patients make that 6-month cutoff?

**RABARA:** Personally, I think most of them do. I’d say probably greater than 50%, in my experience.

**STINCHCOMBE:** Is that consistent with other people’s experience?

**NATHWANI:** We have half of patients [who are platinum sensitive].

**OSEI-BOATENG:** That sounds about right.

**MOHAMED:** Yes, it’s very clear, even from the frontline clinical trial, even with the immune therapies, that PFS [progression-free survival] is around 5 months.

**STINCHCOMBE:** Yes, right. I think that it also depends on when you scan. I tend to personally scan for the first 2 cycles, and the fourth cycle, then I space them out a little bit. So that might bias me;

*continued on page 41*
MONJUVI®
tafasitamab-cxix | 200mg
for injection, for intravenous use

MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant

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).

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend tafasitamab-cxix (MONJUVI) in combination with lenalidomide as a second-line or subsequent therapy option for DLBCL in patients who are not candidates for transplant.1

1It is unclear if tafasitamab or loncastuximab tesirine or if any other CD-19 directed therapy would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

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.

DLBCL=diffuse large B-cell lymphoma; NCCN=National Comprehensive Cancer Network.

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 fever, chills, rash, 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.
SECURE RESPONSE IN SECOND LINE

MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant

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).

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont’d)

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.
1-YEAR PRIMARY ANALYSIS

HIGH ORR REACHED, with a majority of responders achieving CR

1-year primary analysis in patients with R/R DLBCL (N=71)

Best ORR: 55% (n=39; 95% CI: 43%, 67%)
CR: 37%
PR: 18%

SUSTAINED REMISSION in patients with R/R DLBCL

1-year primary analysis in patients with R/R DLBCL (N=71)

Median DoR: 21.7 months (range: 0, 24)

3-YEAR FOLLOW-UP ANALYSIS

MONJUVI, in combination with lenalidomide, was granted accelerated approval based on the 1-year primary analysis of the L-MIND study. The data for the 3-year analysis of the L-MIND study has not yet been submitted to or reviewed by the FDA. The status with respect to potential inclusion of these data in the final, FDA-approved labeling has yet to be determined.

1This analysis is exploratory in nature, and L-MIND was not designed or powered to evaluate and compare multiple subgroups. These results should be interpreted with caution given the small sample size, which may lead to estimates that are unstable.

2Assessed by an Independent Review Committee.1,3

3Kaplan-Meier estimates.1,3

4Due to rounding, ORR percentages may not correspond with the sum of CR and PR percentages.

The cutoff date for the primary analysis was November 30, 2018 and occurred after the last patient enrolled had completed 12 months of follow-up. The cutoff date for the 3-year follow-up analysis was October 30, 2020 and occurred after the last patient enrolled had completed 35 months of follow-up.3,4

R/R=relapsed/refractory; ASCT=autologous stem cell transplant; ORR=best overall response rate; DoR=duration of response; CR=complete response rate; CI=confidence interval; PR=partial response rate; NR=not reached.

ORR (3-year analysis)

3-year follow-up analysis in patients with R/R DLBCL (N=71)

Best ORR: 54% (n=38; 95% CI: 41%, 66%)
CR: 35%
PR: 18%

Response rates in 2L and 3L+ (3-year analysis)

3-year follow-up analysis in patients with R/R DLBCL (N=71)

2L (n=35)

Patients who had received 1 prior therapy

43% CR
63% ORR (n=22; 95% CI: 45%, 79%)
20% PR

3L+ (n=36)

Patients who had received 2 or more prior therapies

28% CR
44% ORR (n=16; 95% CI: 28%, 62%)
17% PR

Median DoR (3-year analysis)

3-year follow-up analysis in patients with R/R DLBCL (N=71)

Median DoR: 43.9 months (95% CI: 15.0, NR)
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.

MONJUVI® (tafasitamab-cxix)

**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 2. Severe fever, chills, rash, 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 for at least 3 months after 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%). Infected-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 are 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;
- Cycle 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 ≥5% 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 95% 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%), 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>37</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>12</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>12</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>12</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>12</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>12</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>12</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>Black pain</td>
<td>19</td>
<td>2.5</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>2.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Fatigue includes asthenia and fatigue

+Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection

†Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal

‡ Rash includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash pustular

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 (2.1%)
- Nervous system disorders: headache (9%), paresthesia (7%), dysesthesia (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%)
Table 4 summarizes the laboratory abnormalities in L-MIND.

Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>MONJUVI&lt;sup&gt;1&lt;/sup&gt; All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>1.4</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>1.4</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time increased</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

<sup>1</sup>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-enhanced 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 hematologic evaluation is completed.

**Data**

**Animal Data**

Animal reproductive studies have not been conducted with tafasitamab-cxix.

**Lactation**

**Risk Summary**

There are no data on the presence of tafasitamab-cxix in human milk. A study of animals has shown that 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.

**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.
During the single-arm, open-label basket trial of lurbinectedin in patients with small cell lung cancer, the overall response rate was 35.2% (95% CI, 26.2%-45.2%). The disease control rate was 68.6% (95% CI, 58.8%-73.3%). The median duration of response was 5.3 months (range, 4.1-6.4). The percentage of patients responding after 6 months was 43.0% (range, 25.6%-60.5%).

should I do a scan at 3 months? Or earlier if symptoms dictate? Now this patient has had a durable benefit of 7 months.

**POLLING QUESTION**

“What would you most likely recommend for this patient outside of a clinical trial?”

- Platinum rechallenge 67% (7)
- Lurbinectedin 18% (2)
- Topotecan 9% (1)
- Other 9% (1)
- Other single-agent chemotherapy 0% (0)
- Cyclophosphamide, doxorubicin, vincristine 0% (0)

Total votes: 11

**MOHAMED**: A question on this patient: Did he continue maintenance immunotherapy, and then he progressed after 7 months?

**STINCHCOMBE**: For this discussion, yes, he was on maintenance therapy. For the participants who chose platinum rechallenge, perhaps we can ask one of you to explain your rationale.

**PATI**: [I would choose platinum rechallenge] since it was more than 6 months, so hopefully the patient will still be sensitive to platinum.

**STINCHCOMBE**: Then, for someone who chose lurbinectedin [Zepzelca], why don’t you explain why you chose it.

**KATRAGADDA**: I chose lurbinectedin just because it’s more tolerable, easy to administer, and has reasonably good response rates in that setting, about 40% [From the Data]. I had good experiences with it, so that’s 1 other thing. It’s also much better than topotecan.

**STINCHCOMBE**: [Dr Hanna], could you explain why you chose topotecan?

**HANNA**: I chose topotecan because I feel this patient is platinum resistant. After 7 months, this patient had high-volume, multiple-organ disease. I just felt this is not a typical 6-month period, so to speak, so I felt maybe he'll get a better response if I use a different agent, so I chose topotecan. At this point, in the second line, there is nothing good for those patients, but I had a good experience with topotecan. I’ve used lurbinectedin before. Maybe I’m better at managing adverse events [AEs] for topotecan than lurbinectedin.

**KUZMA**: We have clinical trials for all stages of relapsed SCLC, but I would choose platinum rechallenge otherwise.

**MOHAMED**: When you have platinum rechallenge, do you keep the immune therapy, or do you change it, or do you discontinue it?

**STINCHCOMBE**: I would do the platinum/etoposide/immunotherapy, then immunotherapy maintenance. Then if they make it for longer than 6 months, my cutoff—I realize that that’s debatable—I will do platinum/etoposide alone, because they’ve progressed on immunotherapy, and I think there’s no evidence of retreatment with immunotherapy at this point or continuing treatment beyond progression in this disease. I have not done that. What do others do?

**RABARA**: I probably would skip the immunotherapy as well and just do the platinum and etoposide.

**STINCHCOMBE**: It’s a good question, though I don’t think anyone knows the appropriate answer. Dr Thomas, would you re-treat with immunotherapy?

**THOMAS**: No, I would not. I agree with exactly what you said you would do: I’d drop the immunotherapy, and then I would rechallenge with etoposide and carboplatin.

**STINCHCOMBE**: I think the National Comprehensive Cancer Network [NCCN] guidelines reflect the sentiment of the group, if you look at it. For relapse before 6 months, the preferred therapies are topotecan, lurbinectedin, or a...
clinical trial. For relapse beyond 6 months, the original regimen is the standard at this point. The NCCN guidelines give you lots of flexibility for other options that people may use at this point. I’ve used CAV [cyclophosphamide, doxorubicin (Adriamycin), and vincristine] in the third-line setting; in a healthy patient, that’s an active combination. I think the challenge with this disease is that topotecan was approved in 1996 and lurbinectedin was approved in June 2020. So outside of immunotherapy, we’ve not had a lot of new drugs approved, particularly—until lurbinectedin was approved in June of 2020, we didn’t have any new drugs in the second-line setting with FDA approval. Remember that doxorubicin was very promising for a period of time; that didn’t work out, so this is a challenging area of drug development.

**DISCUSSION QUESTIONS**

- In your experience, what are the outcomes with platinum rechallenge for platinum-sensitive ES-SCLC (ie, chemotherapy-free interval of at least 6 months)?
- What factors would influence you to use or not use each therapeutic option as second-line therapy? These include platinum-free interval, tolerance to prior therapy, frailty, and comorbidities.

**MADADI:** I usually see around 2 to 3 months when they initially respond, and after 2 or 3 cycles you definitely start seeing progression.

**STINCHCOMBE:** So it has a reasonable response rate, but not the durability; seems to be less time to relapse than the first time.

**OSEI-BOATENG:** Yes, I was going to say the same thing. Usually, by 4 cycles, they’ve started to progress. That’s the typical longest that I’ve seen.

**STINCHCOMBE:** I would say, also, I think the myelosuppression’s slightly worse the second time, in my experience, but that might just be my patient population.

**STINCHCOMBE:** Is there any first-line toxicity that would prevent retreatment, or any event that would make you think that this patient is not a candidate for double-agent therapy, and maybe needs something else?

**RABARA:** If the patient tolerated platinum very poorly initially, I may be hesitant on rechallenging them with the same regimen. I may just go to lurbinectedin in that case.

**STINCHCOMBE:** Now what do you all do with your performance status 2 patients? Does the borderline performance status affect your question of double agent vs single agent?

**MOHAMED:** Yes, patients on the later stage, after the first line, they don’t do well. Their bone marrow was already suppressed with the first-line therapy. So if I have a patient with a performance status of 2, initially I would treat that patient because I know that I can control the disease and get them to feel better with the front line. But a [patient with a] performance status of 2 on the second- and third-line setting is unlikely to do well compared to the first line.

**STINCHCOMBE:** If you have you used lurbinectedin, what types of patients have you used it for? How do you consider it for patients who are platinum sensitive?

**MOHAMED:** I have used it in many of my patients. I did not see an impressive PFS; the response rate was acceptable the first few cycles but gets lost after that. It’s an option that I’m going to continue to use, because I have not used topotecan since I finished my fellowship, and I’m not planning to use it. So definitely, it’s an option for me.

**KATRAGADDA:** I think it’s my preferred second-line treatment. Even if the response rates and toxicities are similar, it’s just not quite as unpopular as topotecan.

**PATI:** I agree with my previous colleagues that it’s much easier than topotecan.

**STINCHCOMBE:** Has the toxicity profile matched what was reported in the trial?

**KATRAGADDA:** I think topotecan has much more myelotoxicity and the chance of neutropenic infections [is greater] compared with lurbinectedin.

**STINCHCOMBE:** Do you use a granulocyte colony-stimulating factor prophylaxis when you use the lurbinectedin?

**KATRAGADDA:** I have not. I have used it only in patients who already had beaten-up bone marrow and a low white blood cell count to start with. I have used it on 1 patient, probably—that’s it. Otherwise, they do pretty well without it.

**RABARA:** I have only had limited experience with it so far, so I haven’t had an extensive experience like others have.
OSEI-BOATENG: I’ve used it in a few patients. I like it better in the second line because it’s much better tolerated compared with topotecan. I’ve only had to use growth factors in 1 patient. I never start out with growth factor support but I had to use it in a patient who ended up with neutropenic fever. So overall, I like it, and I think it’s my go-to second-line drug.

STINCHCOMBE: Do people use the platinum-free interval to triage the lurbinectedin as a choice? What are people’s thoughts on that?

OSEI-BOATENG: Yes, I typically use the 6 months. My go-to is to rechallenge; I think it’s just a matter of trying to use all the options you have. Eventually, it buys you another 3 or 4 months before you get to second line, if their performance status is still decent, and they tolerate it well.

KUZMA: We participated in the ATLANTIS trial [NCT02566993] with 2 patients, and neither did particularly well. In my experience, the few times I have used it now that it’s FDA approved, is that usually at the time of first assessment, radiographic assessment, they have progressed. However, it is a lot easier to give than 5-day-a-week topotecan that usually requires growth factor support.

DISCUSSION QUESTIONS

- Would your approach for next lines of therapy differ if this patient had brain metastasis?
- What is your approach to follow up for patients on second or later lines of therapy?

MORSE: Irinotecan does have some CNS [central nervous system] penetration, and some of my patients with extrapulmonary SCLC have had brain metastases. So I think that’s useful, but I don’t know enough of the data on lurbinectedin. Are you confident of its CNS effects?

STINCHCOMBE: I don’t think it’s been formally assessed at this point because the phase 2 trial excluded those patients.¹ I do think it’s interesting that the brain metastasis can be a problem in this patient population with multiple sites of progression. Sometimes, I’ve used temozolomide [Temodar], which is not a great drug, but was developed for CNS penetration. So I guess the question is what is the third-line therapy?

MOHAMED: Dr Morse brings a good point: You could always use irinotecan as a single agent in the third-line setting. Before the approval of lurbinectedin, and for patients who have platinum-sensitive disease, sometimes I used the combination of cisplatin at reduced doses and irinotecan, and I actually had impressive responses with this regimen.

I have not used it recently, because of lurbinectedin’s approval, but it was a good choice for me with a reduced dose on day 1 and 8 every 3 weeks, and I have had great responses with it. So I appreciate that Dr Morse brought this back to life, because we have used it. Or you can use it as single-agent irinotecan.

STINCHCOMBE: I’ve used it as well, and some people do very well, it seemed, after relapsing. Sometimes you need something that has some activity. But it’s not a tolerable schedule, no.

I think that reflects NTN [non–triple negative]: It gives you a wide flexibility because after you’ve gone through the FDA approvals, there’s not a lot of options that are clear cut better than the others.

DISCUSSION QUESTION

In light of the small proportion of patients who receive 3 lines of therapy for ES-SCLC, how do you view sequencing a mechanism of action switch followed by platinum rechallenge, vs platinum rechallenge followed by mechanism of action switch?

MORSE: I like the idea of extending the interval between the platinum treatments and doing a mechanism of action switch first.

THOMAS: I just think the drugs are so ineffective in general in these second- and third-line patients. I don’t know. I guess you’d have to study it and figure out which one is more effective. I couldn’t say that I would prefer one or the other at this point, based on the lack of a clinical trial.

MOHAMED: Just to be on the opposite side of Dr Morse, I will choose platinum rechallenge followed by mechanism of action switch. I think if it’s more than 6 months, I think platinum challenge is a reasonable option to start with, and then you leave the other option for later.

KUZMA: In my experience, the patients who make it to the third line are those who got the second-line platinum rechallenge because they had a long interval. Usually, it’s almost always, in my experience, the ones that start with platinum rechallenge before trying a mechanism of action switch. I think we tried extending the platinum-free interval, in ovarian cancer, and that didn’t work out particularly well.

¹Reference: [Research article or trial data]
OSEI-BOATENG: In my experience, by the time patients get to third line, their performance status is also not that great for platinum rechallenge. I find that those who’ve had 6 months, they’re still in pretty good shape.

STINCHCOMBE: Yes, I think this interval is both prognostic and predictive of some of the benefit. And so I echo what other people have said: They’ve had a robust response to platinum, then robust response to the second-line therapy. You even start to wonder, is this SCLC, because if they do well, it makes you question the diagnosis.

We have clinical trials for this. It can be challenging to get this third-line population on a clinical trial, between the organ dysfunction, the performance status, and other aspects. So I think this is definitely an unmet need in a challenging patient population.

DISCUSSION QUESTIONS

• What do you view as the most critical unmet needs for patients with ES-SCLC?
• Which emerging data/ongoing studies in ES-SCLC are most interesting to you?

OSEI-BOATENG: An area I struggle with is selecting the best choice for those with brain metastasis.

KATRAGADDA: I agree with the brain metastasis and the myelosuppression. Going back to that, has anybody had experience using that CDK4 inhibitor with the carboplatin, or platinum regimen? It’s been approved for a while now, I think.6

STINCHCOMBE: Trilaciclib [Cosela].

MOHAMED: Yes, I have used it a lot. It’s already built into our care plan. Dr Katragadda and I are on the same system, so it’s available for us to use. I have used it in around 10 or 11 patients. Actually, I’ve got good results, so that’s reassuring.

RABARA: I recently started using it; so far, I only have 2 patients on it. And so far, I haven’t seen much neutropenia since I started using it first line.

MADADI: I have used it, too. I think neutropenia is helped by pegfilgrastim [Neulasta], but it also helps with the thrombocytopenia, which sometimes can lead to a lot of dose reductions. And using it is definitely being a protection for myelosuppression, and reducing the thrombocytopenia has been helpful, too.

STINCHCOMBE: What emerging studies are you most interested in, in ES-SCLC?

MOHAMED: I will be interested in anything that can work in SCLC. It has been a very challenging disease for the last 25 to 30 years, unfortunately. The progress is very mild and slight. Immunotherapy definitely is a great advance. I hope that we can build on that.

STINCHCOMBE: I think some of the trials that are in development. I’m not promoting this trial—we don’t have it at Duke—but Amgen has a bispecific T-cell engager trial [NCT03319940]. It’s opened at [Winship Cancer Institute at Emory University, which might be an option for that, and we’re trying to get it at Duke in the future. This has shown a response rate in refractory patient populations.6 It does have the cytokine release syndrome, but it’s only on the first cycle.

We do have an antibody-drug conjugate. About 50% of people express the protein so we need either an old or new biopsy. I think there’s some interest in liposomal irinotecan; that’s another trial [NCT03088813] that’s going on globally, building on Dr Morse’s and others’ love for irinotecan. But the idea is that liposomal drugs will have better release, better pharmacokinetics, and may have more efficacy.

So I think those are some of the agents that are in development right now, for ES-SCLC, that we’re trying to keep an eye on. Then I think there’s some additional trials looking at different sequencing questions, potentially different timing of lurbinectedin in the maintenance setting. There’s the phase 3 trial [SKYSCRAPER-02; NCT04256421] of carboplatin/etoposide/atezolizumab with or without a T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains drug, and that’s a phase 3 trial that would look at a 4-drug immunotherapy vs carboplatin/etoposide/atezolizumab regimen. ■

REFERENCES

LENVIMA + everolimus is the only TKI-mTOR inhibitor combination following anti-angiogenic therapy in advanced RCC\(^1\,^2\)

**INDICATION**
LENVIMA is indicated in combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

**SELECTED SAFETY INFORMATION**

**Hypertension.** In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

**Cardiac Dysfunction.** Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Arterial Thromboembolic Events.** Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

**Hepatotoxicity.** Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis, and hepaticorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Renal Failure or Impairment.** Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

**Proteinuria.** In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Diarrhea.** Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

See a spectrum of results

Let LENVIMA change the way you view treatment in second-line advanced RCC

- 14.6-month median PFS (95% CI: 5.9-20.1) with LENVIMA + everolimus vs 5.5 months (95% CI: 3.5-7.1) with everolimus alone (HR: 0.37 [95% CI: 0.22-0.62])\(^1\)
  - 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm
**14.6-month median PFS:** with LENVIMA + everolimus vs everolimus alone

![Graph showing PFS probability over time for LENVIMA + everolimus and everolimus arm]

- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm
- 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus alone
- Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus alone

**The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs with an observed HR of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm.**

**Study 205 randomized 153 patients with advanced or metastatic renal cell carcinoma who had previously received anti-angiogenic therapy 1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (≤11.5 g/dL vs >11.5 g/dL for males and ≤13 g/dL vs >13 g/dL for females) and corrected serum calcium (≤10 mg/dL vs <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other efficacy outcome measures included overall survival and objective response rate.**

**SELECTED SAFETY INFORMATION**

**Warnings and Precautions (cont’d)**

**Fistula Formation and Gastrointestinal Perforation.** Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

**QT Interval Prolongation.** In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QTc interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

**Hypocalcemia.** In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Visit [www.LENVIMA.com/hcp](http://www.LENVIMA.com/hcp) to learn more.

**LENVIMA**

(levatinib capsules) 10 mg and 4 mg

---

**Please see all Selected Safety Information throughout and accompanying brief summary of full prescribing information.**
LENVIMA® is a registered trademark used by Eisai Inc. under license from Eisai R&D Management Co., Ltd. © 2021 Eisai Inc. All rights reserved. Printed in USA/September 2021 LENV-US6662

LENVIMA® (lenvatinib capsules) is a prescription medicine used to treat certain types of cancer.

SELEcTede SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CTOd)

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events of any grade occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g., carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 38% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH level was observed post baseline in 70% of LENVIMA–treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week 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 LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ. Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Adverse Reactions

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus–treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions or were diarrhea (21%), fatigue (6%), thrombocytopenia (6%), vomiting (6%), nausea (6%), and proteinuria (6%). Treatment discontinuation due to an adverse reaction occurred in 25% of patients.

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (Clcr 60-89 mL/min) or moderate (Clcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC (endometrial carcinoma) and severe (Clcr <15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC and moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

Please see Brief Summary on the following pages.

**LENVIMA** (lenvatinib) capsules BRIEF SUMMARY – See package insert for full prescribing information.

**INDICATIONS AND USAGE**
LENVIMA is a kinase inhibitor that is indicated:

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
- For the treatment of adult patients with advanced renal cell carcinoma (RCC), in combination with pembrolizumab.
- For the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

**Dosage and Administration**

- **Dose adjustment** may be required based on hematologic and/or clinical parameters. Patients may experience dose delays, reductions, and discontinuations due to adverse reactions.
- Use LENVIMA with caution in patients with moderate or severe hepatic impairment, as recommended dose modifications may be necessary.
- Use LENVIMA with caution in patients with moderate or severe renal impairment, as recommended dose modifications may be necessary.

**Renal Cell Carcinoma (RCC)**

- **Combination Therapy:**
  - In combination with pembrolizumab, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
  - In combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

**Hepatocellular Carcinoma (HCC)**

- **Combination Therapy:**
  - In combination with pembrolizumab, for the treatment of adult patients with advanced hepatocellular carcinoma (HCC) that is not suitable for surgical resection or ablation.

**Endometrial Carcinoma (EC)**

- In combination with pembrolizumab, for the treatment of adult patients with advanced endometrial carcinoma (EC) that is not suitable for surgery or radiation.

**Important Dosage Information**

- **Warning:** Administer LENVIMA with caution in patients with severe hepatic impairment (Child-Pugh C). Patients with severe hepatic impairment who receive LENVIMA should be evaluated every 3 to 4 months for signs of hepatic failure.

**DOSAGE FORMS AND STRENGTHS**

- **Tablet (Orange-Brown) 10 mg**
  - Each tablet contains:
    - Lenvatinib (lenvatinib mesylate) equivalent to 10 mg lenvatinib
  - Dosage is indicated in the table below.

**Table 1: Recommended Dosage Modifications for LENVIMA for Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modifications for LENVIMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Grade 3</td>
<td>Withhold until Grade 0 or 1 baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Cardiac Dysfunction</td>
<td>Grade 3</td>
<td>Withhold until improves to Grade 0 or 1 baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Renal Failure or Impairment</td>
<td>Grade 3</td>
<td>Withhold until improves to Grade 0 or 1 baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Grade 3 or 4</td>
<td>Withhold until less than or equal to 2 grams of proteinuria per 24 hours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue for nephrotic syndrome.</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Fistula Formation</td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Greater than 500 ms or greater than 60 ms increase from baseline</td>
<td>Withhold until improves to less than or equal to 488 ms or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td>Reversible Posterior Leukocytosis Edema</td>
<td>Any Grade</td>
<td>Withhold until fully resolved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose or discontinuation due to severity and persistence of neurologic symptoms.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Persistent or intractable</td>
<td>Withhold until improves to Grade 0 or 1 baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 laboratory abnormality</td>
<td>Resume at a reduced dose.</td>
</tr>
</tbody>
</table>

**Table 2: Recommended Dosage Reductions of LENVIMA for Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Current Dosage</th>
<th>Recommended Dosage Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>10 mg orally once daily</td>
<td>6 mg orally once daily</td>
</tr>
<tr>
<td>HCC</td>
<td>4 mg orally once daily</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8 mg orally once daily</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 mg every other day</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

- **Hypertension:** Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily.
- **Renal Failure or Impairment:** Renal failure or impairment can occur in patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) or with severe renal impairment (creatinine clearance less than 30 mL/min). In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA.
- **Cardiac Dysfunction:** Cardiac dysfunction can occur with LENVIMA, including effects on the right ventricle. Monitor cardiac function before starting LENVIMA and periodically during treatment.
- **Hepatotoxicity:** Serious and fatal hepatic dysfunction can occur with LENVIMA. Across clinical trials in 793 patients with DTC, RCC, or HCC, hepatotoxicity (including hepatocellular, hepatic necrosis, hepatic failure, or hepatic failure, acute hepatic failure, acute liver failure, hepatic necrosis, or hepatic failure) occurred in 17% of patients treated with LENVIMA.
- **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients with RCC and HCC receiving LENVIMA and pembrolizumab. Patients should be monitored for signs of arterial thromboembolic events and treated as appropriate.
- **Hepatotoxicity:** Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than RCC, severe hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis, and hepatic necrosis, occurred in 0.5% of patients.
- **Diabetes:** In REFLECT (DTC), hepatic encephalopathy (including hepatic encephalopathy, hepatic failure, and hepatic failure, acute hepatic failure, acute liver failure, hepatic encephalopathy, and hepatic encephalopathy, hepatic encephalopathy) occurred in 18% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of patients treated with LENVIMA and 2% of patients treated with sorafenib. Grade 5 hepatic encephalopathy occurred in 0.5% of patients treated with LENVIMA and 0.1% of patients treated with sorafenib.
- **Serious Infections:** In a study enrolling patients with RCC, 7% of patients receiving LENVIMA had a serious infection, including pneumonia, which was fatal in 1 patient.
- **Lung Cancer:** In a study enrolling patients with NSCLC, 1 patient experienced lung cancer.
- **Renal Failure or Impairment:** Renal failure or impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients treated with sorafenib in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 totally in 1 patient in each study. In Study 205 (RCC), renal failure or impairment occurred in 18% of patients receiving LENVIMA with everolimus, including in 3% of patients in Study 205 (RCC).

**Further Reading:**

- National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
The safety of LENVIMA was evaluated in SELECT, in which patients with radioactive iodine-refractory differentiated thyroid cancer were randomized (2:1) to LENVIMA (n=261) or placebo (n=131). The median treatment duration was 16.1 months for LENVIMA. Among 261 patients who received LENVIMA, median age was 64 years, 52% were females, 80% were White, 18% were Asian, and 2% were Black, and 4% were Hispanic/Latino.

The most common adverse reactions observed in LENVIMA-treated patients (>30%) were, in order of decreasing frequency: hypertension, fatigue, diabetes mellitus, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-planter erythrodysesthesia (PPE) syndrome, abdominal pain, and dyspnea. The most common serious adverse reactions (at least 2%) were pneumonia (5%), hypertension (3%), and dehydration (2%). Adverse reactions led to dose reductions in 88% of patients receiving LENVIMA; 18% of patients discontinued LENVIMA for adverse reactions. The most common adverse reaction (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asparaginase (1%).

Table 3 presents adverse reactions occurring at a higher rate in LENVIMA-treated patients having received placebo in the double-blind phase of the study.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 24 mg</th>
<th>Placebo N=131</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensiona</td>
<td>33</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal bowel</td>
<td>37</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>Stomatitisb</td>
<td>43</td>
<td>65</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal painc</td>
<td>31</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>29</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Oral pain</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17</td>
<td>0.4</td>
<td>8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>67</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Serum electrolyte concentration</td>
<td></td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>62</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased glomerular filtration rate</td>
<td>64</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>31</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td>33</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmoplantar erythrodysesthesia</td>
<td>32</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>33</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>13</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory and Mediastinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Sputum</td>
<td>12</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>12</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cutaneous infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Other laboratory abnormalities with a difference of ≥2% in Grade 3-4 events and at a higher incidence in the LENVIMA Arma,b in SELECT (DTC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA N=261</th>
<th>Placebo N=131</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (AST)</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase (ALT)</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased cholesterol</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Lab abnormality with a difference of ≥2% in Grade 3-4 events and a higher incidence in the LENVIMA Arm is presented in Table 4.

Table 4: Laboratory Abnormalities with a Difference of ≥2% in Grade 3-4 Events and a Higher Incidence in the LENVIMA Arm in SELECT (DTC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA N=261</th>
<th>Placebo N=131</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (AST)</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase (ALT)</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased cholesterol</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* With at least 1 grade increase from baseline
* Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post-treatment laboratory measurement for each parameter. LENVIMA (n=253 to 258); Placebo (n=129 to 131)

The following laboratory abnormalities (all Grades) occurred in ≥5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypokalemia, increased alkaline phosphatase, hypomagnesemia, hypokalemia, hyponatremia, hyperchloremia, hyperkalemia, hyperglycemia, hypercholesterolemia, increased serum amylose, and hyperhaptoglobinaemia.
Tables 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in 17 months (range 0.1-38).

**Table 5. Adverse Reactions in >20% of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=355</th>
<th>Sumitom 50 mg N=340</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>83 (23)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68 (19)</td>
<td>66 (20)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>53 (15)</td>
<td>36 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (10)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>37 (10)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (7)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>25 (7)</td>
<td>19 (6)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>54 (15)</td>
<td>41 (12)</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>57 (16)</td>
<td>32 (9)</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (16)</td>
<td>43 (13)</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>27 (8)</td>
<td>26 (8)</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>41 (12)</td>
<td>31 (9)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>29 (8)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>29 (8)</td>
<td>38 (11)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N = 343 to 349</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>30 (8)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Acute tubular injury</td>
<td>21 (6)</td>
<td>16 (5)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>30 (8)</td>
<td>9 (3)</td>
</tr>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N = 343 to 349</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23 (6)</td>
<td>16 (5)</td>
</tr>
</tbody>
</table>

*Includes asthenia, fatigue, lethargy and malaise
*Includes diaphoresis and gastrointestinal
*Includes epistaxis, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral, dental, or mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis
*Includes abdominal discomfort, abdominal pain, abdominal tenderness, anorexia, anorexia nausea, back pain, and upper abdominal pain
*Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal dysfunction, musculoskeletal stiffness, myalgia, neck pain, pericardial pain, pain in extremity, and pain in jaw
*Includes hypertension, increased blood thyroid stimulating hormone and secondary hypothyroidism
*Includes arterial hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypotension, tachycardia, and diastolic blood pressure
*Includes acute kidney injury, heart rate that occurred in 1 or more subjects in either treatment group include: Anorexia, cholestasis, ileus, jaundice, malaise, fever, jaundice, nausea, vomiting, and weight loss

**Table 6. Laboratory Abnormalities in >20% (All Grades) of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)**

<table>
<thead>
<tr>
<th>Laboratory Abnormality*</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=62</th>
<th>Everolimus 10 mg N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>80 (24)</td>
<td>78 (24)</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>64 (20)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>61 (19)</td>
<td>34 (11)</td>
</tr>
<tr>
<td>Increased creatine</td>
<td>59 (18)</td>
<td>41 (13)</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>59 (18)</td>
<td>41 (13)</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>58 (18)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>55 (17)</td>
<td>48 (16)</td>
</tr>
<tr>
<td>Increased alanine transaminase (ALT)</td>
<td>54 (16)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>54 (16)</td>
<td>48 (16)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>52 (15)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>44 (13)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>44 (13)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Increased Lactate</td>
<td>42 (12)</td>
<td>35 (12)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42 (13)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>29 (9)</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>29 (9)</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>25 (7)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25 (7)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Hyperoxygenase</td>
<td>23 (7)</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>21 (6)</td>
<td>21 (7)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54 (16)</td>
<td>56 (18)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>39 (12)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38 (11)</td>
<td>38 (12)</td>
</tr>
<tr>
<td>Eosinopenia</td>
<td>34 (10)</td>
<td>34 (12)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>61 (19)</td>
<td>61 (20)</td>
</tr>
<tr>
<td>Increased alanine transaminase (ALT)</td>
<td>58 (18)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>52 (15)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>44 (13)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Increased Lactate</td>
<td>42 (12)</td>
<td>35 (12)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42 (13)</td>
<td>36 (12)</td>
</tr>
</tbody>
</table>

Clinically relevant adverse reactions (<20%) that occurred in patients receiving LENVIMA/pembrolizumab were myocardial infarction (3%) and angina pectoris (1%).
Table 7: Adverse Reactions Occurring in ≥15% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCT)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=62</th>
<th>Everolimus 10 mg N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria/Urinary protein present</td>
<td>31 8</td>
<td>14 2</td>
</tr>
<tr>
<td>Renal failure event</td>
<td>18 10</td>
<td>30 0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Medialistical</td>
<td>37 0</td>
<td>30 0</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>18 0</td>
<td>4 0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>35 5</td>
<td>40 0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension/High blood pressure</td>
<td>42 13</td>
<td>10 2</td>
</tr>
<tr>
<td>Hemorrhagic event</td>
<td>16 0</td>
<td>12 0</td>
</tr>
</tbody>
</table>

In Table 8, Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA with everolimus arm are presented.

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in ≥3% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCT)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=62</th>
<th>Everolimus 10 mg N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 18</td>
<td>18 18</td>
</tr>
<tr>
<td>Increased Epaas</td>
<td>13 12</td>
<td>13 12</td>
</tr>
<tr>
<td>Hypoketolamias</td>
<td>11 0</td>
<td>11 0</td>
</tr>
<tr>
<td>Hypophosphatasias</td>
<td>11 6</td>
<td>11 6</td>
</tr>
<tr>
<td>Hyperkalémia</td>
<td>6 2</td>
<td>6 2</td>
</tr>
<tr>
<td>Hypocalciemia</td>
<td>6 2</td>
<td>6 2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5 2</td>
<td>5 2</td>
</tr>
<tr>
<td>Increased urateaminotransferase (AST)</td>
<td>3 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Increased alanineaminotransferase (ALT)</td>
<td>3 2</td>
<td>3 2</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>3 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>3 1</td>
<td>3 1</td>
</tr>
<tr>
<td>Increased creatine kinase</td>
<td>3 4</td>
<td>3 4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10 20</td>
<td>10 20</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 10</td>
<td>6 10</td>
</tr>
</tbody>
</table>

Hepatocellular Carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomized (1:1) patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=488) or sorafenib (n=476). The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight ≥60 kg and 8 mg orally once daily for patients with a baseline body weight <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was 38 months in 47% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 476 patients who received LENVIMA in REFLECT, the median age was 63 years, 89% were men, 28% were White and 70% were Asian.

The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemoptysis, lip hemorrhage, renal hemorrhata, and scrotal hematoma.

Table 9: Adverse Reactions Occurring in ≥10% of Patients in the LENVIMA Arm in REFLECT (HCC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 8 mg/12 mg N=476</th>
<th>Sorafenib 800 mg N=476</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>21 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 4</td>
<td>46 4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30 3</td>
<td>28 8</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 4</td>
<td>14 1</td>
</tr>
</tbody>
</table>

In Table 10, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Table 10: Grade 3-4 Laboratory Abnormalities Occurring in ≥2% of Patients in the LENVIMA Arm in REFLECT (HCC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA (%)</th>
<th>Sorafenib (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased GGT</td>
<td>17 10</td>
<td>17 10</td>
</tr>
<tr>
<td>Hypoketolamia</td>
<td>15 9</td>
<td>15 9</td>
</tr>
<tr>
<td>Increased phosphate</td>
<td>13 10</td>
<td>13 10</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>12 10</td>
<td>12 10</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>7 5</td>
<td>7 5</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>3 1</td>
<td>3 1</td>
</tr>
<tr>
<td>Increased urateaminotransferase (AST)</td>
<td>4 1</td>
<td>4 1</td>
</tr>
<tr>
<td>Increased alanineaminotransferase (ALT)</td>
<td>1 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>1 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Increased creatine kinase</td>
<td>1 0</td>
<td>1 0</td>
</tr>
</tbody>
</table>

Endometrial Carcinoma

The safety of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant setting. Patients with endometrial carcinoma that are not MSI-H or dMMR received LENVIMA 20 mg orally once daily with pembrolizumab 200 mg intravenously every 3 weeks for 342; or received placebo or placebo (n=320). For patients with not MSI-H or dMMR status, the median duration of study treatment was 7.8 months (range 1 day to 26.8 months) and the median duration of exposure to LENVIMA was 6.7 months (range 1 day to 26.8 months).

The most common serious adverse reactions (≥2%) in patients receiving LENVIMA and pembrolizumab, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pericardial effusion, pleural effusion, pulmonary embolism, and respiratory distress syndrome.

Table 11: Adverse Reactions Occurring in ≥10% of Patients in the LENVIMA and Pembrolizumab Arm in Study 309 (Continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 8 mg/12 mg N=476</th>
<th>Pembrolizumab 200 mg N=476</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>21 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 4</td>
<td>46 4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30 3</td>
<td>28 8</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 4</td>
<td>14 1</td>
</tr>
</tbody>
</table>

(continued)
Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common (≥5%) adverse reactions resulting in dose reduction of LENVIMA were hypertension (11%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (6%), decreased appetite (6%), and weight decreased (5%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (5%) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (6%), decreased appetite (6%), vomiting (6%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.9%), urinary tract infection (2.5%), increased aspartate aminotransferase (2.3%), anesthesia (2.3%), and palmar-plantar erythrodysesthesia (2%). Tables 11 and 12 summarize adverse reactions and laboratory abnormalities, respectively, in patients receiving LENVIMA in Study 309.

<table>
<thead>
<tr>
<th>Table 11: Adverse Reactions in ≥20% of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction</strong></td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
</tr>
<tr>
<td>Hypothyroidismg</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>General</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nervous System</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td><strong>Laboratory Abnormality</strong></td>
</tr>
<tr>
<td><strong>Endometrial Carcinoma (not MSI-H or dMMR)</strong></td>
</tr>
<tr>
<td>LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342</td>
</tr>
<tr>
<td>Doxorubicin or Paclitaxel N=325</td>
</tr>
<tr>
<td><strong>Laboratory Abnormalities Worsened from Baselinea Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)</strong></td>
</tr>
<tr>
<td><strong>Table 12: Laboratory Abnormalities Worsened from Baseline^ occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)</strong></td>
</tr>
</tbody>
</table>

*With at least 1 grade increase from baseline.

**Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: LENVIMA/pembrolizumab range: 312 to 404 patients and doxorubicin or paclitaxel (N=38)

*Grade per NCI CTCAE v4.03

Postmarketing Experience The following adverse reactions have been identified during post approval use of LENVIMA. 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.

Gastrointestinal: pancreatitis, increased amylase

Hematologic: cholecytosis

Renal and Urologic: nephrotic syndrome

Vascular: arterial (including aneurysm) aneurysms, dissections, and rupture

Drug Interactions

Drugs That Prolong the QT Interval LENVIMA has been reported to prolong the QT/QTc interval. Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval.

Use in SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib did not cause adverse effects at doses less than or equal to 0.03 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose of level of 0.1 mg/kg/day (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA).

Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma. Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment with LENVIMA and for at least 1 week after the last dose.

Data

Animal Data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses ≥0.3 mg/kg (approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)) to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail anomalies), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). All oral daily administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroperitoneal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.1 mg/kg/day (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA).

Data

Animal Data

Following administration of radioactive/labeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher (based on area under the curve (AUC)) in milk compared to maternal plasma.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the status of females of reproductive potential prior to initiating LENVIMA.

Contraception

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Infertility

LENVIMA may impair fertility in males and females of reproductive potential.

Pediatric Use

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

Clinical Pharmacology

Animal Data

Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight) and decreased food consumption, and decreases in the width and/or length of the femur and tibia, and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the human exposure based on AUC at the recommended clinical dose of 24 mg). Decreased length of the femur and tibia persisted following 8 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including decreased bone size at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions occurred at earlier treatment time-points in juvenile rats.

Table 12: Laboratory Abnormalities Worsened from Baseline^ occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)
Geriatric Use Of the 261 patients with differentiated thyroid cancer (DTC) who received LENVIMA in
SELECT, 40% were ≥65 years of age and 11% were ≥75 years of age. No overall differences in safety or
effectiveness were observed between these subjects and younger subjects.
Of the 352 patients with renal cell carcinoma (RCC) who received LENVIMA with pembroluzumab in CLEAR,
45% were ≥65 years of age and 13% were ≥75 years of age. No overall differences in safety or effectiveness
were observed between these elderly patients and younger patients.
Of the 82 patients with RCC who received LENVIMA with everolimus in Study 205, 64% were ≥65 years of
age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in
safety or effectiveness between these subjects and younger subjects.
Of the 476 patients with hepatocellular carcinoma (HCC) who received LENVIMA in REFLECT, 44% were
≥65 years of age and 12% were ≥75 years of age. No overall differences in safety or effectiveness were
observed between patients ≥65 and younger subjects. Patients ≥75 years of age showed reduced tolerability
to LENVIMA.
Renal Impairment No dose adjustment is recommended for patients with mild (Clcr 60-89 mL/min) or
moderate (Clcr 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with
DTC, RCC, and endometrial carcinoma and severe (Clcr 15-29 mL/min) renal impairment. Reduce the dose for
patients with DTC, RCC, and endometrial carcinoma and severe renal impairment. There is no recommended
dose of LENVIMA for patients with HCC and severe renal impairment. LENVIMA has not been studied in
patients with end stage renal disease.
Hepatic Impairment No dose adjustment is recommended for patients with HCC and mild hepatic impairment
(Child-Pugh A). There is no recommended dose for patients with HCC with moderate or severe hepatic
impairment.
No dose adjustment is recommended for patients with DTC, RCC, and endometrial carcinoma and mild or
moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC,
RCC, and endometrial carcinoma and severe hepatic impairment (Child-Pugh C). Reduce the dose for patients
with DTC, RCC, and endometrial carcinoma and severe hepatic impairment.
OVERDOSAGE Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan
dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.

LENVIMA® is a registered trademark of Eisai R&D Management Co., Ltd. and is licensed to Eisai Inc.
© 2021 Eisai Inc. All rights reserved. Printed in USA/September 2021 LENV-US6519
Traina Discusses Components of the ASCENT Trial in Patients With TNBC

CASE

- A 48-year-old woman with T1-N1 triple-negative breast cancer (TNBC) received adjuvant dose-dense doxorubicin and cyclophosphamide plus paclitaxel, which she tolerated well.
- Eight months after completion of adjuvant therapy, she reported worsening fatigue.
- Laboratory results: alanine aminotransferase level, 1.5 times the upper limits of normal; aspartate aminotransferase, 1.5 times the upper limits of normal.
- CT scan showed 1 liver and 2 left lung lesions.
- Biopsy of liver lesion confirmed recurrent metastatic TNBC.
- Brain MRI was negative for brain metastasis.
- Genetic panel testing: negative for detectable mutations
- PD-L1 (immunohistochemistry pharmDx): 0% combined positive score
- No significant comorbidities; otherwise healthy
- ECOG performance status: 0
- The patient received frontline gemcitabine plus carboplatin, with a documented partial response lasting 6 months.
- After 6 months of therapy, she reported worsening fatigue.
- Disease progression and new metastasis in the liver were discovered.
- ECOG performance status: 1

Targeted Oncology™: What are the National Comprehensive Cancer Network (NCCN) guidelines for sacituzumab govitecan-hziy (Trodelvy) in TNBC? TRAINA: The NCCN guidelines were updated, and sacituzumab is on there as a preferred regimen, specifically for patients with TNBC. Though it is not a category 1 recommendation, we expect we’ll probably be seeing data to come. But it’s for patients who’ve had at least 2 prior therapies, one of those in the metastatic setting.

What were the data that led NCCN to recommend an antibody-drug conjugate like sacituzumab govitecan in patients with TNBC? This is based on the randomized phase 3...ASCENT study [NCT02574455], which recruited patients who had metastatic TNBC and had received 2 or more prior chemotherapy regimens for advanced disease, with no upper limit. There were some heavily pretreated patients in this trial. More than 500 patients with a 1:1 randomization of sacituzumab vs treatment of physician’s choice [TPC]. TPC on the study essentially covered many of the agents in the guidelines: eribulin [mesylate (Halaven)], vinorelbine [Navelbine], capecitabine [Xeloda], gemcitabine—often the agents we most commonly reach for in the second- and third-line setting.

The primary end point was progression-free survival [PFS], and [they looked at] all the usual secondary end points [overall survival (OS), overall response rate (ORR), duration of response (DOR), and safety]. Generally, [the study population was] young women, early 50s, good performance status to be able to be on a clinical trial, some with germline BRCA1 or BRCA2 mutations, accounting for about 8% of the population. About 70% of these patients had triple-negative disease from the beginning, as opposed to someone who had an estrogen receptor [ER]–positive primary disease and then a triple-negative metastasis. The median time from diagnosis of metastatic disease to coming on study was just over a year, speaking to that rapid tempo of progression, knowing that these folks were largely in the third line of treatment and later. Sixty-one patients had had brain metastases at baseline [that were] treated.

For the baseline characteristics in the primary efficacy population, burden of disease [was] largely visceral lung and liver disease. Patients had a median of 3 prior lines of chemotherapy, but upward of 16 prior regimens of...
therapy for advanced disease. It’s remarkable to think of 16 regimens for use. The prespecified stratification factors for prior chemotherapy regimens was 2 or 3 prior or more than 3. So about 70% of patients were exposed to 2 or 3 prior chemotherapy regimens, and 100% of these patients had prior treatment with a taxane. But most had seen prior anthracycline, cyclophosphamide, and even platinum and capecitabine before coming on study. Fortunately, there’s alignment between the percentage of folks who had germline BRCA mutations and the percentage of folks that got prior PARP inhibitors, about 8%.

**Please describe the efficacy on this trial for patients with TNBC.**

As [I mentioned], the primary end point was PFS. Sacituzumab was superior, with about a 60% improvement in PFS [HR, 0.41; 95% CI, 0.32-0.52; \( P < .0001 \)]. The patients getting TPC did poorly here, with a 1.7-month median PFS [95% CI, 1.5-2.6]. Sacituzumab was associated with almost a 6-month median PFS [95% CI, 4.3-6.3]. So clearly, both a statistically significant and clinically meaningful improvement in PFS. But I think also what was incredibly encouraging [were] the OS data, [and OS] was a secondary end point. There was about a 50% improvement in OS, which was statistically significant [HR, 0.48; 95% CI, 0.38-0.59; \( P < .0001 \)]. A doubling from about 6.5 months [with TPC] to 12 months with sacituzumab. So this was exciting and practice changing for our patients.

If you look at the prespecified subgroups, pretty much every category was favoring sacituzumab over TPC. That was regardless of age, prior regimens, sites of visceral disease or sites of metastases, and whether [the] initial tumor was triple negative or ER positive. When we look at ORR, the waterfall plots look terrific. We’re getting a bit spoiled seeing these with antibody-drug conjugates. So nearly all patients that were treated with sacituzumab derived some degree of benefit, a complete response, definitely clinical benefit overall of 45%...compared with 9% with TPC. Median DOR was double at 6 months...compared with about 3 months. Pretty much by all metrics evaluated, sacituzumab was superior.

**How did patients with brain metastases do on the ASCENT trial?**

The primary end point [we’ve reviewed so far] was efficacy in a specified population that excluded those patients with brain metastases. [Now let’s discuss] the primary end point of PFS in the full intention-to-treat [ITT] population, including those patients who had stable, treated brain metastases. The benefit is maintained in the ITT population as well, with sacituzumab appearing superior to TPC and the hazard ratio, again, consistent with about a 60% improvement in PFS [HR, 0.43; 95% CI, 0.35-0.54; \( P < .001 \)].

**What was the safety profile for sacituzumab govitecan?**

Safety is clearly something to discuss and to be aware of in the balance. Quality of life is important for our patients in making choices, and we need to keep adverse events [AEs] in mind. The most common AEs are cytopenias and gastrointestinal [GI] toxicities.

Neutropenia was common, and grade 3 neutropenia accounted for about 34% with sacituzumab vs 20% with TPC. The component related to febrile neutropenia was, fortunately, much lower, with 5% grade 3 febrile neutropenia with sacituzumab as opposed to 2% with TPC.

In terms of GI events, diarrhea is the AE to be aware of. Knowing that the payload here is a metabolite of irinotecan [Camptosar], grade 3 diarrhea is quite common with irinotecan. But with sacituzumab, it was about 10% grade 3, and much less common with treatment of physician’s choice chemotherapy. But this is an AE that we can mitigate, we can educate around, and we can use supportive strategies to be able to manage.

**Can you describe efficacy with the different TPC options used on this trial?**

Joyce O'Shaughnessy, MD, presented data on this at the 2021 ASCO [American Society of Clinical Oncology] Annual Meeting [Figure]. The majority of physicians reached for eribulin; half chose to prescribe eribulin in this setting. Very few chose vinorelbine, capecitabine, or gemcitabine. But regardless of TPC choice, sacituzumab was superior.
Across the board, sacituzumab performed better than those TPC options. This feels consistent with what we would have done pre-sacituzumab, using eribulin as one of our most active drugs, particularly in TNBC. Although sacituzumab is looking like it’s superior, I don’t know that we could say much about the TPC arms in a head-to-head comparison here. I think this all looks pretty consistent with what physician practice would be in the drugs that we choose. 3

**How does germline BRCA status affect TPC vs sacituzumab govitecan?**

Germline BRCA status was examined. 4 So caveat here and caution: Very few patients, just 7% or 8% of the population, had known germline BRCA1 or BRCA2 mutations. I would say that the data are consistent, that sacituzumab has activity in those patients who carry germline BRCA mutations. Response rates were about 35% compared with 5%. The median PFS hazard ratio is about 0.40, favoring sacituzumab over TPC, and median OS [hazard ratio was 0.48] favoring sacituzumab over TPC—even in those with germline BRCA mutations. It had small numbers, but I think just consistent with the overall trial results.

**Is TROP2 expression important when you are determining if patients with TNBC should receive sacituzumab govitecan?**

This is a question that we hear a lot. Whether TROP2 expression is important, or do we need to test for TROP2 to know whether sacituzumab is an option. The FDA indication is regardless of a companion diagnostic, and this analysis looked at TROP2 expression divided by high, medium, and low scoring. 4, 5 Across the board, regardless of TROP2 expression, sacituzumab appeared to perform better than TPC. 4 Even if you’re looking at TROP2 low, sacituzumab is better. Now, the numbers are small and these are all unplanned analyses, but it is encouraging to see that there appears to be activity regardless. TROP2 is highly expressed across epithelial cancers, across even other breast cancers, triple negative as well as ER positive. So I think the takeaway here is that we do not need TROP2 as a biomarker for choice and activity in using sacituzumab.

**Were the outcomes with sacituzumab govitecan different in patients 65 years and older?**

Kevin Kalinsky, MD, MS, presented these data at ASCO, looking specifically at the subset of patients 65 years and older compared with those younger than 65 years. 6 There were fewer than 100 patients who were [older than] 65 in the study. But in totality, the efficacy looked consistent with the overall study population. The ORR was quite high at 50% with sacituzumab vs 0% with TPC [in those 65 years and older]. Median PFS looked prolonged with a hazard ratio of 0.2 and it was statistically significant [95% CI, 0.12–0.40; P < .0001].

I don’t know that I would read so much into this as much as saying it appears to have consistent efficacy that looks like the overall ITT population. I think what’s reassuring is the safety piece of this. [Although] dose modifications were more frequent in patients that were older, the modifications were similar, whether you were getting sacituzumab or TCP chemotherapy. 5, 6 There didn’t appear to be an impact on efficacy with dose modification. Treatment discontinuations were comparable and rare, 2% whether you were [older than 65 years or younger than 65 years]. Thankfully, there were no grade 5 events [related to treatment]. There were some patients studied that were older than 75 years, and rates of AEs were comparable if you were older than 75 vs older than 65.

I think it just gives us some comfort in knowing that the drug has activity, that it has a reasonable safety profile, and that we should not be discriminating based on age but being sensitive to performance status and comorbidities as our driver, not just chronologic age. Some of the most common treatment-related AEs were consistent with the overall population; neutropenia and cytopenias are common. But that is true for sacituzumab as well as TPC. About 10% grade 3 diarrhea with sacituzumab and rare with TPC.

**REFERENCES**

Roundtable Discussion: Wagner-Johnson Highlights New and Emerging Approaches for DLBCL

CASE SUMMARY

A 75-year-old man presented with fever, a 7-lb unintentional weight loss, and occasional chest pain. He had a medical history of medically controlled hypertension, cardiac failure, and atrial fibrillation, and a physical exam showed he appeared tired and a palpable bilateral cervical lymphadenopathy.

LABORATORY RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydrogenase</td>
<td>300 U/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.8 g/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.3 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.7 mg/dL</td>
</tr>
<tr>
<td>HIV and hepatitis B/C</td>
<td>Negative</td>
</tr>
<tr>
<td>All other values</td>
<td>Within normal limits</td>
</tr>
</tbody>
</table>

LYMPH NODE BIOPSY

An immunohistochemistry panel showed he was CD10 positive and CD20 positive, which confirmed diffuse large B-cell lymphoma (DLBCL). Fluorescence in situ hybridization showed he was negative for rearrangements of BCL6, BCL2, and MYC. A whole-body PET/CT scan showed activity in multiple lymph nodes above and below the diaphragm (largest node, 3.9 cm) and evidence of subcutaneous tissue involvement. An MRI of the brain showed no evidence of lesions. He was diagnosed with International Prognostic Index high-risk stage IV, Ann Arbor stage III/IV disease, with an ECOG performance status of 1.

DISCUSSION QUESTION

What are the key factors that influence your decision-making for next-line therapy?

WAGNER-JOHNSON: I would be interested to hear what is driving your decisions [in a patient case like this]. Other than the general gestalt of the patient, are there certain things that push you one way or another?

PROOTHI: Well, the eligibility for allogenic transplant is one [factor]; eligibility for CAR [chimeric antigen receptor] T-cell therapy is another. Then [I consider] the safety and tolerability of the regimen, comorbidities, patient preference, logistics—I think every item matters.

WAGNER-JOHNSON: Yes, it is sort of a combination of things. If you have a patient for whom you would consider CAR T-cell therapy, what things do you try to avoid as your second-line regimen?

EFIOM-EKHAHA: One of the things [to consider] in terms of second-line...
IMFINZI + EP: The only IO combination with 3-year overall survival in 1L ES-SCLC

Durvalumab (IMFINZI®) + etoposide with either cisplatin or carboplatin is a Category 1, preferred treatment option for first-line ES-SCLC²†

See the new 3-year analysis at IMFINZIhcp.com/sclc

ES-SCLC=extensive-stage small cell lung cancer; EP=etoposide and either carboplatin or cisplatin; IO=immuno-oncology; 1L=first line.

*Preferred intervention=intervention that is based on superior efficacy, safety, and evidence, and, when appropriate, affordability. Category 1=based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate. 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. To view the most recent and complete version of the guideline, go online to NCCN.org.

†See the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for detailed recommendations, including other preferred treatment options.

**NEW CASPIAN THREE-YEAR OVERALL SURVIVAL ANALYSIS**

- The CASPIAN study is an open-label, multicenter, Phase III study of 805 treatment-naïve patients with ES-SCLC who were randomized 1:1:1 between 3 arms. Patients received IMFINZI 1500 mg plus either carboplatin or cisplatin and etoposide Q3W (n=268) for 4 cycles, followed by IMFINZI 1500 mg Q4W until disease progression or unacceptable toxicity or either carboplatin or cisplatin for 2 cycles, and then IMFINZI 1500 mg Q4W until disease progression or unacceptable toxicity. The second arm was EP plus either carboplatin or cisplatin (n=269) for 4 to 6 cycles. The third arm was IMFINZI plus an Investigational Agent and EP followed by IMFINZI maintenance (n=268).

- FDA approval was based on the results from the planned interim analysis of the IMFINZI + EP and EP alone arms. Overall survival was the primary endpoint.

- At the time of the planned interim overall survival analysis with a median duration of follow-up of 14.2 months, mOS was 13 months (95% CI, 11.5-14.8) with IMFINZI + EP vs 10.3 months (95% CI, 9.3-11.2) with EP alone (HR=0.73; 95% CI, 0.59-0.91; P=0.0047).

- At the time of the planned interim overall survival analysis with a median duration of follow-up of 39.4 months, mOS was 12.9 months (95% CI, 11.3-14.7) with IMFINZI + EP vs 10.5 months (95% CI, 9.3-11.2) with EP alone (HR=0.71; 95% CI, 0.60-0.86).

- OS rates at 12, 24, and 36 months are 84%, 74%, and 64% with IMFINZI + EP vs 77%, 65%, and 54% with EP alone, respectively.

- Discontinuation rates were the same with IMFINZI + EP and EP alone (9% in both arms).

- The most common adverse reactions (occurring in ≥20% of patients) were nausea, fatigue/asthenia, and alopecia.

- The most frequent serious adverse reactions reported in ≥1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients).

- Immune-mediated reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions.

Please see Brief Summary of complete Prescribing Information on adjacent pages.
IMFINZI + EP: Sustained overall survival benefit at 3 years

OVERALL SURVIVAL AT 3-YEAR PLANNED EXPLORATORY ANALYSIS

**(median duration of follow-up 39.4 months)**

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Probability of overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>[0.2, 0.6]</td>
</tr>
<tr>
<td>12 months</td>
<td><strong>52.8%</strong></td>
</tr>
<tr>
<td>24 months</td>
<td><strong>22.9%</strong></td>
</tr>
<tr>
<td>36 months</td>
<td><strong>17.6%</strong></td>
</tr>
</tbody>
</table>

HR=0.71 (95% CI, 0.60-0.86)

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>IMFINZI + EP (n=268)</th>
<th>EP (n=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>268</td>
<td>269</td>
</tr>
<tr>
<td>12-24 months</td>
<td>244</td>
<td>243</td>
</tr>
<tr>
<td>24-36 months</td>
<td>214</td>
<td>212</td>
</tr>
<tr>
<td>36-51 months</td>
<td>177</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SUPERIOR OVERALL SURVIVAL AT INTERIM ANALYSIS

**13-MONTH mOS WITH IMFINZI + EP**

VS

**10.3-MONTH mOS WITH EP ALONE**

HR=0.73 (95% CI, 0.59-0.91; P=0.0047)

Safety and tolerability

- Serious adverse reactions occurred in 31% of patients receiving IMFINZI + EP at the interim analysis and in 33% of patients receiving IMFINZI + EP at the 3-year analysis.
- The most frequent serious adverse reactions reported in ≥1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and chronic obstructive pulmonary disease (1.1%).
- The most common adverse reactions (occurring in ≥20% of patients) were nausea, fatigue/asthenia, and alopecia.
- Discontinuation rates were the same with IMFINZI + EP and EP alone (9% in both arms).
- Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI + EP. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients).

---

1 The planned exploratory 3-year OS analysis was conducted at ~3 years after the last patient was randomized, and was not formally tested for statistical significance. At the time of the 3-year analysis, mOS was 12.9 months (95% CI, 11.3-14.7) with IMFINZI + EP vs 10.5 months (95% CI, 9.3-11.2) with EP alone (HR=0.73; 95% CI, 0.59-0.91). OS rates at 12, 24, and 36 months are the estimated proportion of patients alive based on the 3-year analysis.

2 The CASPIAN study is an open-label, multicenter, Phase III study of 805 treatment-naive patients with ES-SCLC who were randomized 1:1:1 between 3 arms. Patients received IMFINZI 1500 mg plus either carboplatin or cisplatin and etoposide Q3W for 4 cycles, followed by IMFINZI 1500 mg Q4W until disease progression or unacceptable toxicity or either carboplatin or cisplatin and etoposide Q3W (n=269) for 4 to 6 cycles. The third arm was IMFINZI plus an Investigational Agent and EP followed by IMFINZI maintenance (n=268). FDA approval was based on the results from the planned interim analysis of the IMFINZI + EP and EP alone arms. Overall survival was the primary endpoint. At the time of the planned interim overall survival analysis with a median duration of follow-up of 14.2 months, mOS was 13 months (95% CI, 11.5-14.8) with IMFINZI + EP vs 10.3 months (95% CI, 9.3-11.2) with EP alone (HR=0.73; 95% CI, 0.59-0.91; P=0.0047).
Select Safety Information (continued)

Immune-Mediated Adverse Reactions (continued)
Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue IMFINZI depending on severity. See Dosing and Administration for specific details. In general, if IMFINZI requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis
IMFINZI can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients who did not receive prior radiation, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. In patients who received recent prior radiation, the incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation within 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (87/475) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475), 1.1% were fatal and 2.7% were Grade 3 adverse reactions. The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar in patients who received IMFINZI as a single agent or with ES-SCLC when in combination with chemotherapy.

Immune-Mediated Colitis
IMFINZI can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2% (9/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 3 (0.4%) adverse reactions.

Immune-Mediated Hepatitis
IMFINZI can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions.

Immune-Mediated Endocrinopathies
- **Adrenal Insufficiency:** IMFINZI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- **Hypophysitis:** IMFINZI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated. Grade 3 hypophysitis/hypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI.
- **Thyroid Disorders:** IMFINZI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.
- **Thyroiditis:** Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- **Hyperthyroidism:** Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI.
- **Hypothyroidism:** Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- **Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis:** Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Grade 3 immune-mediated type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI.

Immune-Mediated Nephritis with Renal Dysfunction
IMFINZI can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

Immune-Mediated Dermatology Reactions
IMFINZI can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), have occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Immune-mediated rash or dermatitis occurred in 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.4%) adverse reactions.

Other Immune-Mediated Adverse Reactions
The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMFINZI or were reported with the use of other PD-1/PD-L1 blocking antibodies.
- **Cardiac/vascular:** Myocarditis, pericarditis, vasculitis.
- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis.
(including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

- **Ocular**: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

- **Gastrointestinal**: Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis.

- **Musculoskeletal and connective tissue disorders**: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.

- **Endocrine**: Hypoparathyroidism

- **Other (hematologic/immune)**: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

### Infusion-Related Reactions

IMFINZI can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue IMFINZI based on the severity. See Dosing and Administration for specific details. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses. Infusion-related reactions occurred in 2.2% (42/1889) of patients receiving IMFINZI, including Grade 3 (0.3%) adverse reactions.

### Complications of Allogeneic HSCT after IMFINZI

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L-1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L-1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/L-1 blocking antibody prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI 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 IMFINZI and for at least 3 months after the last dose of IMFINZI.

### Lactation

There is no information regarding the presence of IMFINZI in human milk; however, because of the potential for adverse reactions in breastfed infants from IMFINZI, advise women not to breastfeed during treatment and for at least 3 months after the last dose.

### Adverse Reactions

- In patients with extensive-stage SCLC in the CASPIAN study receiving IMFINZI plus chemotherapy (n=265), the most common adverse reactions (≥20%) were anemia (34%), fatigue/asthenia (32%), and alopecia (31%). The most common Grade 3 or 4 adverse reaction (≥3%) was fatigue/asthenia (3.4%).

- In patients with extensive-stage SCLC in the CASPIAN study receiving IMFINZI plus chemotherapy (n=265), IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and COPD (1.1%). Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI plus chemotherapy.

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

Please see Brief Summary of complete Prescribing Information on adjacent pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.

### References


**IMFINZI** (durvalumab) injection, for intravenous use

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

**INDICATIONS AND USAGE**

**Small Cell Lung Cancer**

IMFINZI in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

**DOSEAGE AND ADMINISTRATION**

**Recommended Dosage**

The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with chemotherapy are presented in Table 1 [see Clinical Studies (14) in the full Prescribing Information].

IMFINZI is administered as an intravenous infusion over 60 minutes.

**Dosage Modifications for Adverse Reactions**

No dose reduction for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

**Dosage modifications for IMFINZI for adverse reactions that require management different from these general guidelines are summarized in Table 2.**

**Table 1. Recommended Dosages of IMFINZI**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended IMFINZI dosage</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES-SCLC</td>
<td>Patients with a body weight of 30 kg or more: 1500 mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as a single agent</td>
<td>Until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>Patients with a body weight of less than 30 kg: 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 10 mg/kg every 2 weeks as a single agent</td>
<td></td>
</tr>
</tbody>
</table>

*Administer IMFINZI prior to chemotherapy on the same day. When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information.

**Table 2. Recommended Dosage Modifications for Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune-Mediated Adverse Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Grade 2</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanent discontinuation</td>
</tr>
<tr>
<td>Collitis</td>
<td>ALT or AST increases to more than 3 and up to 8 times the ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN</td>
<td>Withhold</td>
</tr>
<tr>
<td>Hepatitis with no tumor involvement of the liver</td>
<td>AST or ALT increases to more than 8 times ULN or total bilirubin increases to more than 3 times the ULN</td>
<td>Permanent discontinuation</td>
</tr>
<tr>
<td>Hepatitis with tumor involvement of the liver*</td>
<td>AST or ALT increases to more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN or</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>AST or ALT increases to more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN</td>
<td>Permanent discontinuation</td>
</tr>
<tr>
<td></td>
<td>AST or ALT increases to more than 10 times ULN or total bilirubin increases to more than 3 times ULN</td>
<td>Permanently discontinues</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Grade 3 or 4</td>
<td>Withhold until clinically stable or permanently discontinue depending on severity</td>
</tr>
<tr>
<td>Nephritis with Renal Dysfunction</td>
<td>Grade 2 or 3 increased blood creatinine</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 4 increased blood creatinine</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Exfoliative Dermatologic Conditions</td>
<td>Suspected SJS, TEN, or DRESS</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Confirmed SJS, TEN, or DRESS</td>
<td>Permanent discontinuation</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Grade 2, 3, or 4</td>
<td>Withhold</td>
</tr>
<tr>
<td>Neurological Toxocities</td>
<td>Grade 2</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

**Other Adverse Reactions**

| Infusion-related reactions (see Warnings and Precautions (5.2) in the full Prescribing Information) | Grade 1 or 2 | Interrupt or slow the rate of infusion |
|                                                                                              | Grade 3 or 4 | Permanently discontinue |

**Preparation and Administration**

**Preparation**

- **Usually inspect drug product for particulate matter and discoloration prior to administration,** whenever solution and container permit. **Discard the vial if the solution is cloudy, discolored, or visible particles are observed.**
- **Do not shake the vial.**
- **Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL.**
- **Discard partially used or empty vials of IMFINZI.**

**Storage of Infusion Solution**

- **IMFINZI does not contain a preservative.**
- **Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the time from preparation should not exceed: 28 days in a refrigerator at 2°C to 8°C (36°F to 46°F) or 8 hours at room temperature up to 25°C (77°F).**
- **Do not freeze.**
- **Do not shake.**

**Administration**

- **Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.**
- **Do not co-administer other drugs through the same infusion line.**

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Immune-Mediated Adverse Reactions**

IMFINZI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2) in the full Prescribing Information]. In general, if IMFINZI requires interruption or discontination, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

**Immune-Mediated Pneumonitis**

IMFINZI can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

**In Patients Who Did Not Receive Recent Prior Radiation**

In patients who received IMFINZI on clinical trials in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 5 patients. Systemic corticosteroids were required in 19 patients (19/34) with pneumonitis who did not receive chemoradiation prior to initiation of IMFINZI.

**In Patients Who Received Recent Prior Radiation**

The incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation for 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (50/272) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475) 1.1% were fatal and 2.7% were Grade 3 adverse reactions. Events resolved in 50 of the 87 patients and resulted in permanent discontinuation in 27 patients. Systemic corticosteroids were required in 64 patients (64/87) with pneumonitis who had received chemoradiation prior to initiation of IMFINZI, while 2 patients required use of inhaled and high-dose steroids. The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar whether IMFINZI was given as a single agent in patients with various cancers in a pooled data set or in patients with ES-SCLC when given in combination with chemotherapy.

**Immune-Mediated Colitis**

IMFINZI can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 2% (37/1888) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 5 (0.4%) adverse reactions. Events resolved in 27 of the 37 patients and resulted in permanent discontinuation in 8 patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 2 patients (0.7%) required other immunosuppressants (e.g. infliximab, mycophenolate).
**Immun-mediated Hepatitis**

**IMFINZI** can cause immune-mediated hepatitis. Immunemediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions. Events resolved in 21 of the 52 patients and resulted in permanent discontinuation of IMFINZI in 6 patients. Systemic corticosteroids were required in all patients with immunemediated hepatitis, while 2 patients (0.2%) required use of mycophenolate with high-dose steroids.

**Immunemediated Endocrinopathies**

Adrenal Insufficiency: **IMFINZI** can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.2) in the full Prescribing Information].

Immune-mediated adrenal insufficiency occurred in 0.9% (17/1889) of patients receiving IMFINZI, including Grade 2 (<0.1%) and Grade 3 (0.1%) adverse reactions. Events resolved in 1 of the 9 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.

Hypophysitis: **IMFINZI** can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.

Withhold or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.2) in the full Prescribing Information].

Grade 3 hypophysitis/hypothalamic/panhypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI. Treatment with system corticosteroids was administered in this patient. The event did not lead to permanent discontinuation of IMFINZI.

**Thyroid Disorders**

**IMFINZI** can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hyperthyroidism or institue medical management of hypothyroidism as clinically indicated. Withhold or discontinue IMFINZI based on the severity [see Dosage and Administration (2.2) in the full Prescribing Information].

Thyroiditis: Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 4 of the 9 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in 3 patients (9/39) with immune-mediated hypothyroidism, while 6 patients (6/39) required endocrine therapy. Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI. Events resolved in 30 of the 39 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in 9 patients (3/9) with immune-mediated hyperthyroidism, while 35 patients (35/39) required endocrine therapy.

Hypothyroidism: Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 31 of the 156 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in 11 patients (11/156) and the majority of patients (152/156) required long-term thyroid hormone replacement. Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.2) in the full Prescribing Information].

Thyroiditis: Grade 3 immune-mediated type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI. This patient required long-term insulin therapy and IMFINZI was permanently discontinued. Two additional patients (0.2%) (2/1000) had events of hyperglycemia requiring insulin therapy that did not resolve at the time of reporting.

**Immunemediated Nephritis with Renal Dysfunction**

**IMFINZI** can cause immune-mediated nephritis.

Immunemediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 5 of the 10 patients and resulted in permanent discontinuation in 3 patients. Systemic corticosteroids were required in all patients with immunemediated nephritis.

**Immunemediated Dermatomyositis**

**IMFINZI** can cause immune-mediated rash or dermatitis.

Immune-mediated rash or dermatitis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 5 of the 10 patients and resulted in permanent discontinuation in 3 patients. Systemic corticosteroids were required in all patients with immunemediated dermatomyositis.

**Other Immune-mediated Adverse Reactions**

The following clinically significant, immunemediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMFINZI or were reported with the use of other PD-1/PD-L1 blocking antibodies.

**Cardiovascular**

- Myocarditis, pericarditis, vasculitis.

**Nervous system**

- Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including myasthenia gravis exacerbation), Guillain-Barré syndrome, HIV-associated encephalopathy.

**Ocular**

- Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

**Gastrointestinal**

- Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis.

**Musculoskeletal and connective tissue disorders**

- Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.
In mouse allogeneic pregnancy models, clinically recognized pregnancies is 2-4% and 15-20%, respectively. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in developing fetus. Apprise pregnant women of the potential risk to a fetus.

Human immunoglobulin G1 (IgG1) is known to cross the confirmation of pregnancy through delivery resulted in an increase in premature delivery, fetal loss (abortion and stillbirth), and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (see Data).

Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data in lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature delivery, fetal loss (abortion and stillbirth), and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

**Lactation**

Risk Summary. There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (see Data).

Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

**Females and Males of Reproductive Potential**

**Contraception**

Females
Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1) in the full Prescribing Information). Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months following the last dose of IMFINZI.

Pediatric Use

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

Geriatric Use

Of the 476 patients treated with IMFINZI in the PACIFIC study, 45% were 65 years or older, while 7.6% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients. The PACIFIC study did not include sufficient numbers of patients aged 75 years and over to determine whether they respond differently from younger patients. Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immunemediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI (see Warnings and Precautions (5.1) in the full Prescribing Information), including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypophysitis.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatological Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermatological reactions.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of aspartic meningitis, immune thrombocytopenia, myositis, myasthenia gravis, dermatomyositis, and myalgic encephalopathy.

Infusion-Related Reactions:

- Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of infusion-related reactions (see Warnings and Precautions (5.2) in the full Prescribing Information).

Complications of Allogeneic HSCT:

- Advise patients of potential risk of post-transplant complications (see Warnings and Precautions (5.3) in the full Prescribing Information).

**Embryo-Fetal Toxicity**

- Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3) in the full Prescribing Information).
- Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI (see Use in Specific Populations (8.3) in the full Prescribing Information).

**Lactation**

- Advise female patients not to breastfeed while taking IMFINZI and for at least 3 months after the last dose (see Warnings and Precautions (5.4) and Use in Specific Populations (8.2) in the full Prescribing Information).

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: AstraZeneca UK Limited, 1 Francis Crick Ave., Cambridge, England CB2 0AA

US License No. 2043

IMFINZI is a registered trademark of the AstraZeneca group of companies.

©AstraZeneca 2021 07/21 US-56258 8/21
therapy is the timing of the relapse, right? I think in [cases of] relapse within 12 months, the outcomes are better with CAR T-cell therapy, and maybe allogeneic transplant would be reasonable for someone who has relapse 5 years out from the initial therapy.

As far as the salvage therapy, if I am thinking about doing CAR T-cell therapy, I want to avoid therapies that [cause] lymphodepletion, as things like bendamustine [Bendeka] probably would not be part of that salvage regimen.

**WAGNER-JOHNSON:** Do others try to avoid bendamustine in the second-line setting for this reason?

**NATHAN:** Yes, I would avoid bendamustine for this reason.

**EFIOM-EKAHA:** Another thought would be [to consider, for example, that] you just, logistically, could not get a patient to CAR T-cell therapy early, [even though] that [might have been] your intention.

Should I also avoid CD19-directed therapies in that setting? Though I know for a fact that CAR T-cell therapy would still work [in the future] if I used loncastuximab [Zynlonta] or tafasitamab [Monjuvi] and [the patient] had a nice response. I do not know the answer to that.

**CASE UPDATE**

The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide [Cytoxan], doxorubicin, vincristine, prednisone), which was well tolerated. A PET scan at the end of treatment showed complete remission, but 1 year later, the patient presented with diffuse lymphadenopathy confirmed by PET/CT scan and a biopsy showed relapse of DLBCL. The patient was considered ineligible for transplant due to older age and high risk. The patient then received second-line therapy consisting of rituximab plus gemcitabine and oxaliplatin; R-GemOx, and he achieved a best response of partial remission. After 5 months, the patient experienced disease progression. CAR T-cell therapy was discussed as an option, but the patient declined due to distance to the nearest transplant center.

**WAGNER-JOHNSON:** [The answer to that question] may reflect [whether the respondent is] from an academic center where they are going to keep [rather than refer] their patients, [and it may also reflect] patient preference and [the overall] patient population. I have heard from people in the community that some of their patients do not have any desire to come and see us [if they are referred here].

**POLLING QUESTION**

“What would you most likely recommend for this patient now, after chemoimmunotherapy?”

- Tafasitamab + lenalidomide 67% (6)
- Polatuzumab vedotin ± bendamustine/rituximab 22% (2)
- Other/clinical trial 11% (1)
- Loncastuximab tesirine 0% (0)
- Rituximab-based chemotherapy 0% (0)

Total votes: 9

**DISCUSSION QUESTION**

- How do you think about the newer treatment options for relapsed/refractory DLBCL (eg, polatuzumab vedotin with or without BR; tafasitamab plus lenalidomide; and loncastuximab tesirine)?
- What individual patient characteristics (clinical or pathological) might make a difference in your assessment?
- When you think about each treatment option, what patient comes to mind as a “perfect fit”?

**WAGNER-JOHNSON:** Some of you definitely have some experience with these regimens. [There is not as much experience with] loncastuximab, if I remember correctly; that was the newer one to be approved.

**RIZVI:** Polatuzumab, in my experience, has been very well tolerated. Generally, for people who are not eligible for transplant or [for] any other treatment option, I have found polatuzumab to be pretty effective and pretty well tolerated.

**WAGNER-JOHNSON:** When you are giving it, do you typically give it with the BR [bendamustine/rituximab] or without?

**RIZVI:** These are patients who are very frail, so I end up giving [polatuzumab] by itself.

**WAGNER-JOHNSON:** Got it—I have not given [polatuzumab] singly yet. I often have given it as a bridge for...
my patients [when they] have had their CAR T cells collected and we are waiting for manufacturing, and I will frequently give, at that point, bendamustine.

At that point, the patients have already had their cells collected, so I am not as concerned, and [these patients] are typically more fit because they are heading to CAR T-cell therapy, and if I need to give bridging, they have [aggressive] disease. But I have not given [polatuzumab] singly yet.

I am pretty sure Dr Gladstone has some experience in that regard. Do you frequently give it [as part of a combination] or not? What is your experience?

GLADSTONE: I always [anguish] about it. Also, when I do use it, [my choice] depends on the disease burden. [That is, it depends on whether] I think I am going to get the patient to collection easily, or [I think] it is going to be very hard because [their disease is] so bulky. I know that does not answer the question, but that [is what] goes into my thinking, even though it is a non sequitur.

WAGNER-JOHNSON: [I see.] Dr Rizvi, you have had good experience [with polatuzumab] as a single agent, per the National Comprehensive Care Network [NCCN] guidelines, [which] clearly indicate [that option]. Who else has had some experience with this regimen and wants to give their thoughts on choosing to give [polatuzumab] with or without the BR?

PROOTHI: I have used it with the rituximab [only], without the bendamustine.

Obviously, if [the patient] had a neurotoxicity a year before, then I would not pick the polatuzumab. If [the patient] has a high-risk [status after] transplant, I would rather go with the loncastuximab; otherwise, I would not have any preference.

The other question I have is, for the tafasitamab plus lenalidomide combination, if the [lenalidomide] dose matters, at 25 mg, and if [the patient] gets grade 4 neutropenia, should I use the growth factor and [maintain] the dose or should I lower the dose?

WAGNER-JOHNSON: I have given growth factors successfully and have been able to maintain [the dose]. I think it frequently happens that [the patient’s neutrophil count] is so, so low that you must [stop treatment] for a bit or lower [the dose]. I usually do not have the luxury of catching [the neutropenia] early, [such that] I can give the growth factor and avoid problems. Often, I do both simultaneously, [and when] I give the growth factor, the counts recover, and then I consider escalating.

I think part of the problem is the logistics of [finding the appropriate] dose for the patient because [every adjustment] requires a new prescription. But I do often try to push [the dose] back up. I have not had as much luck when giving that with just rituximab, and I need to gain some more experience with [tafasitamab].

FAROUN: I am hopeful that, soon, polatuzumab is going to move to frontline therapy for [patients with] DLBCL. I think it is not going to be used in the second line or beyond. So we [will be] left with 2 regimens: loncastuximab [and the combination of] tafasitamab and lenalidomide.

I think if the patient is refractory to rituximab or has germinal centers, we will use tafasitamab plus lenalidomide. I do not have any experience with loncastuximab yet but [I am hopeful that] we can use it in the future, but again, if polatuzumab is moving up [to the first line], I think that will leave us with 2 options only.

WAGNER-JOHNSON: That is a good point. Could we hear from a few more people about their thoughts in terms of which [option] seems the most appealing, or [in terms of] the perfect fit for a particular drug?

PROOTHI: [Regarding] polatuzumab, some centers are taking vincristine out of R-CHOP [and replacing it with] polatuzumab instead.

EFIOM-EKAHA: My concern is that in the community, a lot of times, we want to salvage these patients with CAR T-cell therapy, but logistically, sometimes [it is] a little tricky to get them to CAR T-cell therapy, and so we have inertia. We say that we do not want to use a CD19-targeted drug [because] we do not want to burn the bridge, but while you are trying all kinds of bridging therapies, the disease could be progressing. I [think that] tafasitamab plus lenalidomide, with a 40% complete response [CR] rate and almost a 60% overall response rate, is a great regimen [From the Data].

So I say to myself, why don’t I just use my most active therapy and worry about the logistics of CAR T-cell therapy later rather than be afraid of using a CD19-targeted therapy [just] because I think [the patient] may get to CAR T-cell therapy [eventually]?

GLADSTONE: I believe it is a true statement that the tafasitamab molecule binds to a different section of CD19. But the concern that tafasitamab is going to outcompete rituximab is probably not going to be borne out in the future.

WAGNER-JOHNSON: Yes, and we [have not talked] about bispecific T-cell engager [BiTE] therapies; none of those are currently approved but they look incredibly promising.
It is going to be interesting to see how things develop with respect to naked antibodies, antibody-drug conjugates (ADCs), BiTEs, and CAR T-cell therapies. There is going to be a breadth of available treatments. And from a practical standpoint, if our ADCs compare relatively well with a BiTE, my guess is that most in the community will be more comfortable choosing the ADC. Similarly, we will see whether the BiTEs, especially in combination with other agents, hold up in competition with CAR T-cell therapies. Of course, we do not have mature data to make these statements, but I think it is interesting to look at the CR rates because they are impressive. I think a lot is going to be learned about these novel agents, and where they fit in, with further follow-up in the next few years.

**GLADSTONE:** The thing that is impressive, I think, is that tafasitamab by itself does not get a grade of A-plus. Tafasitamab plus lenalidomide is much better than tafasitamab alone, and for patients who are chemotherapy resistant, it is important to note that bendamustine is chemotherapy, and loncastuximab is not. What is nice about the combination of tafasitamab and lenalidomide is that it is purely immunologic. So if you think a patient’s cancer cells do not have the ability to respond to a chemotherapy signal, tafasitamab plus lenalidomide does not use chemotherapy.

**WAGNER-JOHNSON:** True.

**GAFFAR:** I did use loncastuximab recently for a patient with horrible renal sufficiency and relapsed DLBCL. I did use tafasitamab plus lenalidomide, and then recently I put him on loncastuximab, and he has had a good response so far. As an aside, he did have a repeat biopsy; he has gingival involvement, so they easily biopsied it and found that it was still CD19 positive.

**WAGNER-JOHNSON:** Good. Were there any problems with the unique toxicities that we are seeing, edema or elevation of liver enzymes?

**GAFFAR:** Not really. Maybe a little bit of edema but nothing else.

---

**NEWLY DIAGNOSED FOLLICULAR LYMPHOMA: FRONTLINE TREATMENT DECISIONS**

Daniel Greenwald, MD, from UCLA Health, discusses goals of therapy and variables that affect how patients with newly diagnosed follicular lymphoma are managed with chemoimmunotherapy in the frontline setting, including during COVID-19.

View more at: TargetedOnc.com/link/1831
INDICATION
XPOVIO® (selinexor) is a prescription medicine approved:
- in combination with bortezomib and dexamethasone (XVd) to treat adult patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION
Thrombocytopenia: XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma.

Thrombocytopenia is the leading cause of dosage modifications. Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Monitor patients for signs and symptoms of bleeding. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia: XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection. Monitor more frequently during the first 3 months of treatment. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity: XPOVIO can cause severe gastrointestinal toxicities in patients.

Nausea/Vomiting/Diarrhea: Provide prophylactic antiemetics or treatment as needed.

Anorexia/Weight Loss: Monitor weight, nutritional status, and volume status at baseline and throughout treatment and provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia: XPOVIO can cause severe or life-threatening hyponatremia.

Monitor sodium level at baseline and throughout treatment.

Serious Infection: XPOVIO can cause serious and fatal infections. Atypical infections reported after taking XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Neurological Toxicity: XPOVIO can cause life-threatening neurological toxicities.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities until the neurological toxicity fully resolves. Institute fall precautions as appropriate.
RESTORE YOUR PATIENTS’ OWN CANCER DEFENSES

XPOVIO® is the first and only FDA-approved XPO1 inhibitor that helps restore the body’s own tumor suppressor pathways to fight multiple myeloma (MM) as early as first relapse.¹

XPOVIO combined with bortezomib and dexamethasone (XVd) is approved for adult patients who have received ≥1 prior MM therapy.¹

See the clinical results at xpoviopro.com.

Embryo-Fetal Toxicity: XPOVIO 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 and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Cataracts: New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataract requiring clinical intervention was reported.

ADVERSE REACTIONS

The most common adverse reactions (ARs) (≥20%) in patients with multiple myeloma who received XVd were fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract, and vomiting.

Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

Fatal ARs occurred in 6% of patients within 30 days of last treatment. Serious ARs occurred in 52% of patients. Treatment discontinuation rate due to ARs was 19%. The most frequent ARs requiring permanent discontinuation in >2% of patients included fatigue, nausea, thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting. Adverse reactions led to XPOVIO dose interruption in 83% of patients and dose reduction in 64% of patients.

USE IN SPECIFIC POPULATIONS

No overall difference in effectiveness of XPOVIO was observed in patients >65 years old when compared with younger patients. Patients ≥65 years old had a higher incidence of discontinuation due to an adverse reaction (AR) and a higher incidence of serious ARs than younger patients. The effect of end-stage renal disease (CLCR <15 mL/min) or hemodialysis on XPOVIO pharmacokinetics is unknown.

Please see full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact Karyopharm Therapeutics Inc. at 1-888-209-9326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: 1. XPOVIO (selinexor) [prescribing information]. Newton, MA: Karyopharm Therapeutics Inc.; April 2021.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary is not intended to provide all the information needed to use XPOVIO safely and effectively. Please see XPOVIO Full Prescribing Information at XPOVIOpro.com.

INDICATIONS AND USAGE

XPOVIO is a nuclear export inhibitor indicated:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

WARNINGS AND PRECAUTIONS

Thrombocytopenia

XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia is the leading cause of dosage modifications. Thrombocytopenia was reported in 92% of patients and severe (Grade 3-4) thrombocytopenia was reported in 43%. The median time to first onset was 22 days for any grade thrombocytopenia and 43 days for the Grade 3 or 4 thrombocytopenia. Bleeding occurred in 16% of patients with thrombocytopenia, clinically significant bleeding (Grade ≥3 bleeding) occurred in 4% of patients with thrombocytopenia, and fatal hemorrhage occurred in 2% of patients with thrombocytopenia. Permanent discontinuations of XPOVIO due to thrombocytopenia occurred in 2% of patients.

Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia

XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection.

Neutropenia was reported in 48% of patients and severe neutropenia (Grade 3-4) was reported in 12% of patients. The median time to onset of the first event was 23 days for any grade neutropenia and 40 days for Grade 3-4 neutropenia. Febrile neutropenia was reported in <1% of patients.

Obtain white blood cell counts with differential at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity

XPOVIO can cause severe gastrointestinal toxicities.

Nausea/Vomiting

With use of antiemetic prophylaxis (88% of patients), nausea was reported in 50% of patients and Grade 3 nausea was reported in 8% of patients. The median time to onset of the first event was 6 days. Vomiting was reported in 21% of patients and Grade 3 vomiting was reported in 41%. The median time to onset of the first event was 8 days. Permanent discontinuation due to nausea occurred in 31% of patients and due to vomiting occurred in 21% of patients. Provide prophylactic antiemetics. Administer 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with XPOVIO. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Diarrhea

Diarrhea was reported in 32% of patients and Grade 3 diarrhea was reported in 6% of patients. The median time to onset of the first event was 50 days. Permanent discontinuation due to diarrhea occurred in 1% of patients. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Anorexia/Weight Loss

Anorexia was reported in 35% of patients and Grade 3 anorexia was reported in 3.6% of patients. The median time to onset of the first event was 35 days. Permanent discontinuations due to anorexia occurred in 2% of patients.

Weight loss was reported in 26% of patients and Grade 3 weight loss was reported in 2% of patients. The median time to onset of the first event was 58 days. Permanent discontinuation due to weight loss occurred in 1% of patients. Monitor weight, nutritional status, and volume status at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia

XPOVIO can cause severe or life-threatening hyponatremia. Hyponatremia was reported in 58% of patients and Grade 3-4 hyponatremia was reported in 14% of patients. The median time to first onset was 21 days for any grade hyponatremia and the median time to first onset for Grade 3 or 4 hyponatremia was 22 days.

Monitor sodium level at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Correct sodium deficit as appropriate for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Assess hydration status and manage hyponatremia per clinical guidelines, including intravenous saline and/or salt tablets as appropriate and dietary review. Interrupt, reduce dose or permanently discontinue based on severity of the adverse reaction.

Serious Infection

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia. 69% of patients experienced any grade of infection. Grade ≥3 infections were reported in 32% of patients, and deaths from infections occurred in 3% of patients. The most frequently reported Grade ≥3 infection was pneumonia in 14% of patients, followed by sepsis in 4.1% and upper respiratory tract infection in 3.6%. Atypical infections reported after XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Monitor for signs and symptoms of infection, evaluate and treat promptly.

Neurological Toxicity

XPOVIO can cause life-threatening neurological toxicities. Neurological adverse reactions (excluding peripheral neuropathy) including dizziness, syncope, depressed level of consciousness, vertigo, amnesia and mental status changes (including delirium and confusional state) occurred in 26% of patients and severe events (Grade 3-4) occurred in 3.6% of patients. The median time to the first event was 29 days. Permanent discontinuation due to neurological adverse reactions occurred in 2.1% of patients.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurological toxicity fully resolves. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

Embryo-Fetal Toxicity

XPOVIO 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 and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Cataract

New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataracts requiring clinical intervention was reported in 22% of patients. The median time to new onset of cataract was 228 days and was 237 days for worsening of cataract in patients presenting with cataract at start of XPOVIO therapy. Treatment of cataracts usually requires surgical removal of the cataract.

ADVERSE REACTIONS

Clinical Trials Experience

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

Multiple Myeloma

XPOVIO in Combination with Bortezomib and Dexamethasone (SVd)

The safety of XPOVIO in combination with bortezomib and dexamethasone was evaluated in BOSTON. Patients were randomized to receive XPOVIO 100 mg orally once weekly in combination with bortezomib and dexamethasone (SVd) (n=195) or bortezomib and dexamethasone (Vd) (n=204). Among patients who received XPOVIO, the median duration of XPOVIO treatment was 29 weeks (range: 1 to 120 weeks) and the median dose was 80 mg (range: 30 to 137 mg) per week.

Serious adverse reactions occurred in 52% of patients who received XPOVIO in combination with bortezomib and dexamethasone. Serious adverse reactions in >3% of patients included pneumonia (14%), sepsis, diarrhea and vomiting (4% each). Fatal adverse reactions occurred in 6% of patients within 30 days of last treatment, including pneumonia (n=3) and sepsis (n=3).

Grade ≥2 peripheral neuropathy, a pre-specified key secondary endpoint, was lower in the SVd arm (21%) compared to the Vd arm (34%); odds ratio 0.50 [95% CI: 0.32, 0.79]). The median treatment duration was 30 weeks (range: 1-120 weeks) in patients who received once weekly SVd as compared to 32 weeks (range: 1-122 weeks) in patients who received twice weekly Vd.

Permanent discontinuation of XPOVIO due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation of XPOVIO in >2% of patients included fatigue (3.6%), nausea (3.1%), thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting (2.1% each).
Verify the pregnancy status of females of reproductive potential prior to Pregnancy Testing

XPOVIO can cause fetal harm when administered to a pregnant woman. Advise females not to breastfeed during treatment with XPOVIO and for 1 week after the last dose.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Based on findings in animals and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose (see Dose). Advise pregnant women of the risks to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

**Animal data**

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor, 0.025, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve [AUC] at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

**Lactation**

Risk Summary

There is no information regarding the presence of selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with XPOVIO and for 1 week after the last dose.

**Females and Males of Reproductive Potential**

XPOVIO can cause fetal harm when administered to a pregnant woman.

**Pregnancy Testing**

Verify the pregnancy status of females of reproductive potential prior to initiating XPOVIO.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

**Males**

Advise males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

**Infertility**

**Females and Males**

Based on findings in animals, XPOVIO may impair fertility in females and males of reproductive potential.

**Pediatric Use**

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

**Geriatric Use**

Of the 195 patients with multiple myeloma who received XPOVIO in combination with bortezomib and dexamethasone, 56% were 65 years of age and older, while 17% were 75 years of age and older. No overall differences in effectiveness were observed between these patients and younger patients. When comparing patients 65 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (28% vs 13%) and a higher incidence of serious adverse reactions (56% vs 47%).

**PATIENT COUNSELING INFORMATION**

Advising the patient to read the FDA-approved patient labeling (Medication Guide).

**Dosing Instructions**

- Instruct patients to take XPOVIO exactly as prescribed.
- Advise patients to swallow the tablet whole with water. The tablet should not be broken, chewed, crushed, or divided.
- If a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of XPOVIO, advise them to take the next dose on the next regularly scheduled day.
- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to take their prescribed dexamethasone (if applicable) and prophylactic anti-nausea medications exactly as directed.
- Advise patients that blood tests and body weight will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first 3 months of treatment.
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment.

**Hematologic Adverse Reactions**

**Thrombocytopenia**

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Gastrointestinal Adverse Reactions**

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist.

**Serious Infection**

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever).

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Anemia**

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia.

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Hematologic Adverse Reactions**

**Thrombocytopenia**

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Gastrointestinal Adverse Reactions**

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist.

**Serious Infection**

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever).

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Anemia**

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia.

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Hematologic Adverse Reactions**

**Thrombocytopenia**

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Gastrointestinal Adverse Reactions**

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist.

**Serious Infection**

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever).

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Anemia**

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia.

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Hematologic Adverse Reactions**

**Thrombocytopenia**

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

**Gastrointestinal Adverse Reactions**

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist.

**Serious Infection**

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever).

**Neutropenia**

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.
Targeted Oncology™: What should oncologists know about GVHD?

BISHOP: GVHD is a leading cause of nonrelapse mortality [NRM] following allogeneic stem cell transplant. The No. 1 cause of mortality is, unfortunately, relapse. We now see both acute and chronic GVHD as probably the second leading cause of death and the No. 1 cause of NRM.

Acute GVHD is a reaction of donor immune cells, primarily from the graft, that affect the following 3 tissues in the recipient: skin, liver, and gastrointestinal [GI] tract. Chronic GVHD is a syndrome that has a lot of similarities to autoimmune diseases seen outside the transplant realm. It may involve a single organ or multiple organs. Biologically, [it occurs from] T cells and B cells that arise from the stem cell graft from the bone marrow after engraftment has occurred.

The risk factors for acute and chronic GVHD are very similar. Acute GVHD was considered the greatest risk factor for chronic GVHD, but that’s not necessarily true due to the different ways that we’re doing transplants now, as opposed to the classical way they were done prior to the turn of the century.

With standard GVHD prophylaxis, approximately 25% to 50% of patients who receive a human leukocyte antigen [HLA]-matched stem cell graft will develop GVHD that requires high-dose systemic steroids. Unfortunately, approximately 50% of these patients will have an inadequate response, meaning either a lack of response to treatment or an inability to get off steroids once they achieve a response.

GVHD develops in 3 phases as was described by the work of James L. Ferrara, MD, who has been a leader in our understanding of the biology of acute GVHD. The first phase occurs due to tissue damage from the conditioning regimen leading to an inflammatory response that releases cytokines such as IL-6 and tumor necrosis factor [TNF], and damage within the small intestine leads to release of lipopolysaccharides.¹

These inflammatory cytokines stimulate host antigen-presenting cells [APCs], and those donor T cells that are within the graft see these host antigens presented by the professional APCs and become activated. This leads to the development of type 1 helper T cells, which release inflammatory cytokines such as interferon-γ and IL-2. Concurrently, the lipopolysaccharides get taken up by macrophages, which can lead to further stimulation of T cells. Eventually, the target antigen—be it on skin, the intestinal tract, or the liver—is attacked by these activated cells. All 3 phases are necessary for the activation of acute GVHD.

Our first goal is to prevent GVHD, and there are several ways to go about it. Probably the most traditional way is using calcineurin inhibitors, such as cyclosporine and tacrolimus [Prograf], in combination with methotrexate. Calcineurin inhibitors can also be combined with mycophenolate mofetil and with sirolimus [Rapamune]. Sometimes, a combination of 3 medications is used.

For a long time, people have also used T-cell monoclonal antibodies. Antithymocyte globulin [ATG (Thymoglobulin)] is commonly used, particularly in unrelated donor transplants. But there are also data, particularly from the United Kingdom, on the use of alemtuzumab [Lemtrada] to deplete T cells in vivo.

We can also do ex vivo T-cell depletion by doing CD34 selection in the graft, where the T cells are removed and CD34 cells are maintained. T-cell depletion has long been used to prevent GVHD. A more interesting and back-to-the-past type of treatment is the use of posttransplant cyclophosphamide, which was based upon early work done by George W. Santos, MD, at Johns Hopkins University in the 1970s.

It has been further developed more recently by the Johns Hopkins group to permit the transplantation of haploidentical grafts and is being applied to unrelated donors in HLA-matched sibling grafts with a high degree of success. The problem is, once GVHD develops, there can be difficulties...
in trying to control it with steroids alone. There are several potential targets that one can use to try to control it. There are calcineurin inhibitors such as tacrolimus, cyclosporine, and sirolimus. There are ways to block the T-cell receptor, such as by using ATG. TNF is one of the cytokines that gets activated, and we can think about etanercept [Enbrel] or infliximab [Remicade] to block it. Another T-cell–expressed antigen is CD52, blocked by alemtuzumab.2

For other inflammatory cytokines that get activated during the second phase of GVHD activation, we can look for antibodies that block IL-6 receptors, such as tocilizumab [Actemra], and IL-2 receptors, such as daclizumab [Zinbryta] and basiliximab [Simulect]. Researchers have looked at blocking the cholesterol pathway through atorvastatin [Lipitor], CASP3 blockade, and bortezomib [Velcade] for the proteasome pathway. There is also rituximab [Rituxan] because B cells can be an APC, as well. So, we have several molecules and every one of these has been investigated, either primarily for the treatment of GVHD [or] in some cases the prevention of GVHD.2

What are the risk factors for acute GVHD?
Donor recipient factors include class I and class II major HLA disparity. Looking at minor HLA disparity is not something we commonly do. Then there is sex matching, donor parity, and donor age. For ABO mismatch, there is a slight increase in risk of GVHD but not a big deal. Donor CMV serostatus is a very big deal. But sometimes we will select a CMV-positive donor in the situation where the recipient is also positive. [Individuals] have looked at cytokine gene polymorphisms, but that’s not a common practice in our clinic situation.

For [stem cell graft factors], there is the stem cell source, for example if it is peripheral blood vs bone marrow vs umbilical cord blood. But there are data that make this controversial. For stem cell graft composition, if T cells are depleted, the incidence of GVHD is very low. Researchers haven’t been able to quantitate the perfect T-cell dose.

There are some controversial data about high very CD34 dose, but this is generally when you get to $10 \times 10^7$ CD34/kg cell dose that you start seeing this higher incidence of GVHD. For [conditioning intensity], there is a myeloablative vs a reduced-intensity condition regimen.

What stage/grade GVHD does this patient have? Are there institutional preferences for grading/staging for acute GVHD?
Based on the Mount Sinai Acute GVHD International Consortium [MAGIC] criteria [for organ staging of acute GVHD], this patient, because he had 60% [body surface area involvement], would be put at stage III. The other important thing is how many diarrhea episodes the patient is having. I don’t know how it is at other institutions but getting the nurses to accurately measure [diarrhea volume] has been tough for us. But in an adult, it would be stage I for up to 4 diarrhea episodes a day. When you can’t do an absolute volume measurement, then you can go by the frequency of the episodes. When we take it all together, this patient had stage III rash, and he had stage I lower GI involvement. He would have an overall grade 2, based upon the MAGIC criteria.3

So, [the overall clinical] grade would be 2 at a minimum, but it was an unfair question because they didn’t give us all the information needed. There was the University of Minnesota acute GVHD stratification, which Margaret MacMillan, MD, MSc, had written about as early as 2012.4 But what was more important was its multi-institutional confirmation that was published in 2015. They were able to demonstrate that they could divide GVHD into standard risk vs high risk. Now, fortunately, the high-risk individuals were a small proportion, but it was defined as any involvement of 1 organ with stage IV for the skin, stage III to IV for the gut, and stage I to IV for the liver.5

The reason that [risk stratification] is important is that it correlates with a probability of treatment-related mortality [TRM]. The multi-institutional verification of the [University of Minnesota] stratification plan demonstrated about a doubling in terms of TRM in the high-risk vs standard-risk groups.6

A paper published by John E. Levine, MD, and his colleagues from the University of Michigan looked at a combination of different molecular markers and cytokines, and were able to demonstrate that, based upon this, they could stratify patients into high-risk and low-risk GVHD.4 They looked at these markers during the early onset of the disease. Some researchers have tried to look at this before the disease onset. There is a modified version where they use [TNF], ST2, and REG3, and it seems to correlate well with the Levine et al version in terms of overall survival [OS] and particularly TRM.

What data support the use of ruxolitinib (Jakafi) alongside steroids in steroid-refractory GVHD?
The REACH1 study [NCT02953678] was a [phase 2 trial for patients with steroid-refractory acute GVHD]. They started with ruxolitinib at 5 mg twice a day and maintained steroids. On day 4, if their counts, particularly platelets, were looking fine, they could go straight to 10 mg twice daily. The overall response rate [ORR] was the primary end point.7
The ORR at day 28 was 55%, and the best ORR at any one time was 73%. It was encouraging that the response was generally seen within a week, as early as day 6. The median duration of response [DOR] among responding patients was approximately 11 months. The NRM at 6 months was 44% and the median OS had not been reached.6

This led to the phase 3 REACH2 study [NCT02913261], which was primarily a European study, that had patients with steroid-refractory acute GVHD. What differed from REACH1 is that they started ruxolitinib at 10 mg twice daily. They had a best available therapy [BAT] control arm, chosen by the investigator. It was published in the *New England Journal of Medicine* by Zeiser et al.9

The BAT included ATG, extracorporeal photopheresis [ECP], mesenchymal stem cells, low-dose methotrexate, mycophenolate mofetil, everolimus [Afinitor], sirolimus, etanercept, or infliximab. The most common investigator choice of BAT was in the supplement, and it was ECP, which is interesting. Patients had the ability to cross over, and again the primary end point was ORR at day 28. The key secondary end point was durable ORR at day 56.

The ORR at day 28 was 62% for ruxolitinib vs approximately 40% for investigator-choice BAT [odds ratio (OR), 2.64; 95% CI, 1.65-4.22; P<.001 (Figure)]. The complete response rate for ruxolitinib was almost double that of BAT [at 34% vs 19%, respectively]. The secondary end point of durable ORR at day 56 was 40% for ruxolitinib vs 22% for BAT [OR, 2.38; 95% CI, 1.43-3.94; P<.001]. For the full analysis, they broke it down by grade. Across all grades, even in grade 4 disease, there was an advantage for ruxolitinib. There was an improvement in patients with liver involvement too.

For the DOR, an overwhelming majority of patients in the ruxolitinib arm were compared with those in the control arm. The DOR maintained superiority in the ruxolitinib arm. For significant improvement in staging of the skin, upper GI, lower GI, and liver, ruxolitinib was superior.

The failure-free survival [FFS] was also superior for the ruxolitinib arm. [It was 5 months for ruxolitinib vs 1 month for BAT (HR, 0.46; 95% CI, 0.35-0.60)]. It didn’t quite reach statistical significance but still improved FFS in the ruxolitinib arm.

It is important to know that the relapse was not any higher [for the ruxolitinib arm]. For toxicities, the incidence of thrombocytopenia nearly doubled for [ruxolitinib at 33% vs 18% for the BAT control arm], and that’s not a big surprise. With ruxolitinib, you’d need to monitor [platelet count]. There was a slightly higher incidence of [CMV] infection and I think infections overall with ruxolitinib.

---

**REFERENCES**


A 54-year-old man with a history of metastatic renal cell carcinoma (mRCC) had undergone a left nephrectomy and adrenalectomy. He had clear cell RCC (ccRCC) and metastases in his adrenal gland. Four years later, the patient had a recurrence of his cancer. A biopsy showed lung nodules consistent with ccRCC. In retrospect, it had been present on scans for at least 2 years prior.

The patient was observed based on the low volume and indolence of the disease and on his preference. Eighteen months later, a reexamination showed continued indolent growth on scans, with an increased total tumor burden, and a new paratracheal lymph node (2 × 1.5 cm). A decision was made to initiate systemic therapy with pembrolizumab (Keytruda) plus axitinib (Inlyta).

On follow-up, the patient’s disease was stable. The patient reported moderate diarrhea (well controlled with antidiarrheal medication) and mild fatigue. After cycle 6, he developed fatigue, mild shortness of breath, and mild cough without chest pain. His pulse oximeter reading was 93% at rest. He had no fever and no recent sick contact and his influenza vaccination was up-to-date. His infectious work-up results were negative.

At approximately week 18, a chest CT scan confirmed grade 3 pneumonitis. Pembrolizumab treatment was held and intravenous steroids were administered. Pembrolizumab was then discontinued and the patient continued on axitinib.

Fourteen months after the initiation of systemic therapy, the patient reported increasing back pain, mild nausea, weight loss, and new onset of persistent rib pain. Imaging confirmed disease progression: The paratracheal lymph node had been 20 × 15 mm and was now 25 × 28 mm; there were new mediastinal and hilar nodal involvement, new retroperitoneal nodes, and new lytic lesions. He had an ECOG performance status of 1.

**POLLING QUESTION**

“Which second-line therapy are you most likely to recommend for this patient?”

- **Cabozantinib**: 88% (14)
- **VEGF-TKI combination (eg, lenvatinib/everolimus)**: 12% (2)
- **Immune checkpoint inhibitor regimen (eg, nivolumab/ipilimumab)**: 0% (0)
- **Other**: 0% (0)

Total votes: 16
Case-Based Roundtable Meetings Spotlight

**TUMOR TYPE**

**Barata:** We have a number of factors such as tolerability, toxicity, efficacy, patient preference, guidelines, and type of disease. What would you highlight at this point for considering one therapy vs another? Let us say he [still] has an ECOG performance score of 1.

**Mulherin:** How symptomatic is the patient?

**Barata:** Let's say he is not [very symptomatic]. He is having some weight loss, but not a lot. His tolerability to cabozantinib was OK, a bit of diarrhea, but manageable. He has a bit more fatigue, but not that different from when he was on axitinib 5 months ago. How does this affect your choice?

**Mulherin:** I think we could do lenvatinib [Lenvima] plus everolimus [Afinitor] or tivozanib [Fotivda], either of those would be possibilities. I have used both. I have used tivozanib in a couple of patients who made it that far and were still candidates for treatment. I have not had as many good experiences with everolimus. I know you can mitigate the stomatitis with oral dexamethasone, but I have found that it is not as easy [to tolerate].

**Barata:** Is it everolimus monotherapy or lenvatinib plus everolimus you are referring to?

**Mulherin:** I was thinking about putting them together. If you were going to send them for a clinical trial, he has an ECOG performance score of 1, so he would be a great option for a 2 vs 1 trial. But if I am not going to do that, it would be 1 of those 2.

With an ECOG performance score of 1, he should be able to tolerate the toxicities of either of those regimens. I would be more inclined to do lenvatinib plus everolimus because he would be getting a totally different mechanism of action with an mTOR inhibitor and, ideally, he should be able to tolerate that.

**Ciobanu:** I agree with Dr Mulherin. The only thing that I was thinking is that the response rate of tivozanib is not great, I mean it is [23%] and this patient got only 4 months of response to cabozantinib [From The Data¹]. I do think that in this situation, he is already exposed to a third-generation TKI [tyrosine kinase inhibitor] with axitinib, so probably the best choice for him in terms of a response would be lenvatinib with everolimus because it has a better response rate.²

We do not know the response rate as third-line therapy, but it has a different mechanism of action. As Dr Mulherin mentioned, [lenvatinib plus everolimus] is not an easy regimen to tolerate, so it is unlikely that it will be tolerated better later in the disease course. I think this may be the time to choose it.

**Barata:** Among the different end points, do you favor response rate over measures such as progression-free survival [PFS] or overall survival? Is that your go-to end point when you are thinking of the refractory space, along with quality of life [QOL]?

**Ciobanu:** Yes, response rate [is my favored end point].

**Barata:** Would you be concerned about the tolerability?

**Ciobanu:** If a patient is very symptomatic, [I’d be concerned;] obviously, you want somebody to have a higher chance to respond. But [I’d also like] a longer duration of response. He had only 4 months PFS on cabozantinib. You want something better, and a chance of PFS as well.

**DISCUSSION QUESTIONS**

- What are the goals of therapy going into third-line agents?
- What factors influence your third-line regimen selection in this setting?

**CASE UPDATE**

The patient was given 60 mg of cabozantinib (Cabometyx) once a day. Four months later, disease progression was documented. The patient wanted to continue active therapy.

**FROM THE DATA**

In the randomized TIVO-3 trial (NCT02627963), 41 (23%; n = 175) patients who received tivozanib had an objective response to therapy vs 20 (11%; n = 175) patients who received sorafenib.¹ The median duration of response for tivozanib was 20.3 months (95% CI, 9.8-29.9) vs 9.0 months (95% CI, 3.7-16.6) with sorafenib.

---

¹ From The Data

² From The Data
BARATA: That is fair. Dr Konala, do you agree or do you prioritize other things? Is this combination regimen what comes to mind in this setting? What is the goal of therapy? Do you care about quality of life [QOL]? Do you care about a patient not progressing and tolerating the regimen well?

KONALA: I agree with the prior speakers. Axitinib was tried and tivozanib is [similar]. I would go with lenvatinib and everolimus. If the patient is symptomatic, I would go with response rate because this combination has the highest response rate [of 43%]. They tried axitinib and cabozantinib, but lenvatinib targets a slightly different receptor compared with cabozantinib. Everolimus is an mTOR inhibitor, so it has a different mechanism of action. I have tried this therapy only in 2 patients so far, but it is hard to tolerate. I had to dose reduce [because] I had patients with hypertension and diarrhea. I have used it in very young patients with translocation RCC and they did not respond much to it. However, in the third line, I think it is the best option we have with a different mechanism of action and different receptors being targeted.

POLLING QUESTION

“What third-line therapy are you most likely to consider for this patient upon disease progression?”

- Lenvatinib/everolimus 87% (13)
- Tivozanib 13% (2)
- Pazopanib 0% (0)
- Nivolumab 0% (0)
- Sunitinib 0% (0)
- Other 0% (0)

TOTAL VOTES: 15

BARATA: Dr Baldeo, what would be your thoughts about lenvatinib plus everolimus vs tivozanib?

BALDEO: I have not used tivozanib, but based on the trial, the adverse effects [AEs] look comparable. I have used lenvatinib plus everolimus, and I have always had to dose reduce mainly because of the fatigue and diarrhea.

BARATA: Based on the data, do they favor tivozanib, or not so much?

BALDEO: Well, the dose reduction favors tivozanib because I think [the number of patients needing dose reductions] was more than 70% with the everolimus plus lenvatinib arm. I am not familiar with using it, but I would be willing to give it a try just because it has [fewer] dose reductions, based on the trial.

BARATA: Dr Oppelt, any other thoughts? Of course, we do not have any head-to-head studies. What are your thoughts about putting things into perspective? What is your clinical judgment of the data?

OPPELT: I would echo a lot of what has been said. I think the data are impressive in that it does look like it is a well-tolerated drug in the third-line setting. I think a lot of patients are interested in that. As far as its efficacy, it is impressive that there are patients who are 2 to 4 years out without evidence of progression. I think it is a reasonable option in terms of being aggressive against the disease compared with the lenvatinib and everolimus combination.

BARATA: Dr Bendaly, any comments on the toxicities? Would you feel comfortable with one vs the other?

BENDALY: I am one of the few oncologists not aware of the tivozanib data. I picked lenvatinib plus everolimus in the third-line setting, but after what you shared with us, I think tivozanib would be my go-to third-line agent. My thought process initially was that [tivozanib] has the same activity profile against all the different TKIs as axitinib and we had used axitinib earlier for this patient. So it would not overcome the resistance, especially because both are third-generation TKIs, but the data are compelling. In terms of managing hypertension as the main AE, I think it is not a big drawback.

DISCUSSION QUESTION

To what extent, if any, does consideration of later lines of therapy affect your choice of frontline therapy?

BARATA: Do you think of frontline therapy first and then see what happens? Do you think about what is going to happen in the second-line and third-line settings?

BENDALY: I think about it from the start. I try to use immunoncology [IO] drugs up front and keep TKI options for later. If we use pembrolizumab plus axitinib in the front line, and the patient progresses, we have burned the IO and TKI options for the time being. I understand that some providers might come back and use an IO in later lines. [Based on] the data, and from my experience with this combination for the higher-risk patients, I know some patients end up doing quite well for a very long time. I have not seen this with axitinib and pembrolizumab. Full disclosure, I have not used pembrolizumab and axitinib for as long as I have used the double IO [nivolumab (Opdivo) plus ipilimumab (Yervoy)], probably because they have not been on the market for as long.
To me, it is far more important to be without progression than [to be] looking at the response rate. I do not want tumor shrinkage because it does not matter to me if you have a bunch of lung metastases shrinking 20% vs 30%. I do not think that is clinically significant for a patient in front of me in the third- or fourth-line setting.”

—PEDRO C. BARATA, MD, MSC

BARATA: Are these important data for you to think of post IO, post checkpoint inhibitor, post TKI? What are your thoughts on if that will affect your use of tivozanib in this setting, Dr Spigel? Are these data enough for you to think [of going] with a TKI vs an mTOR such as everolimus?

SPIGEL: I think the data are compelling. I think tivozanib is a good option, but the comparator arm is what troubles me. Sorafenib [Nexavar] is something that feels a little bit antiquated and maybe not the best comparator arm. I like the comments that have been made about switching mechanisms of action. It is just that my experience with everolimus and mTORs in general has been modest. [I view them as] drugs that have a bit of toxicity and not a lot of responses.

I think we are stuck. This is a [case] where you wonder if they got a fair shake with the IO, but you can’t push it because of the pneumonitis. So you are stuck with the VEGF pathway and all the drugs...have overlapping mechanisms of action, and some are probably a little bit better than others. I just think we must keep trying them sequentially and try to squeeze as much out of them as we can, but I think the lenvatinib plus everolimus data are interesting.

BARATA: Does it bother you that the control arm is also everolimus? Although we have lenvatinib alone there too.

SPIGEL: Yes, that is a reasonable control arm in this group. For doublet therapy in a patient who is on the third line and has been on treatment this long, you know you are going to be dose modifying and dropping something quickly. There are not a lot of great options, and probably nothing is going to give you sustained disease control. So you start to think of QOL and try to minimize progression as best as you can.

BARATA: So [you would say that] the data are compelling, but QOL is the important goal in this setting. You want to control disease, but the patient should not be doing poorly while you do that. The goal is to buy time. Is that a fair summary?

SPIGEL: I would call Dr Garmezy first to ask for advice because I work with him. I do not [currently] treat much RCC. I treat a lot of lung cancer, but when I did treat a lot of RCC, I used a ton of bevacizumab [Avastin]. I liked it and it was easy, but I see it is a class [2B] recommendation now. Nobody uses it anymore?

BARATA: Very unlikely. To be honest with you, I also forget the last time I prescribed sunitinib [Sutent] and pazopanib [Votrient].

SPIGEL: Yes, fair enough.

BARATA: Things are changing. Any final thoughts on this, Dr Anwar?

ANWAR: PFS was 3.9 months for sorafenib vs 5.6 months for tivozanib. It is an absolute difference of 1.7 months. But the control arm was sorafenib, which is not an mTOR inhibitor. In your practice, in how many patients on third-line therapy do you use tivozanib vs lenvatinib or anything else?

BARATA: We are talking about a heavily pretreated population. [In the TIVO-3 trial (NCT02627963), 38% in the tivozanib arm and 41% in the sorafenib arm received] 3 lines of prior therapy, whereas [62% in the tivozanib arm and 59% in the sorafenib arm received] 2 lines of prior therapy. So you can see that anything you do will be more limited.

The goal here is not to cure. I do not think we are able to reasonably offer a cure to these patients. Even the response rate depends on how miserable they are going to be. I put things into context and [consider] the goal of care. To me, it
is far more important to be without progression than [to be] looking at the response rate. I do not want tumor shrinkage because it does not matter to me if you have a bunch of lung metastases shrinking 20% vs 30%. I do not think that is clinically significant for a patient in front of me in the third- or fourth-line setting.

The other piece of the story is a lot of these patients are getting IO in the second-line setting too. An mTOR is basically an immunosuppressive drug, and we do not have good data post IO of what happens with lenvatinib plus everolimus. None of these data are perfect, I have to say.

When you look at cabozantinib in the METEOR study [NCT01865747] or nivolumab in the CheckMate 025 study [NCT01668784], the data were for pre-IO agents in the frontline setting. Lenvatinib plus everolimus was pre-IO in the frontline setting too. What we do not know is the activity of that combination post IO. I like the fact that when you look at tivozanib, the data are more contemporary, which means more patients were exposed to a prior checkpoint inhibitor and you had a good number of patients who actually got there.

We know who got checkpoint inhibition there. I would like more data with axitinib and cabozantinib. For tivozanib you have data after checkpoint inhibition, which reflects more of what we do in clinical practice. [Concerning] safety, for my patients, lenvatinib plus everolimus is not [easy]. I do it, but we just need to be aware of the safety profile.

I am not going to tell you what we should do because I am not here to provide advice, but those are some of my thoughts and insights about what options are out there. Because I do not have a head-to-head study to definitively tell you A is better than B, I cannot make that assumption. I shared with you how I interpret the data, but your thoughts and insights are well taken.

GARMEZY: At the 2021 American Society of Clinical Oncology Genitourinary Cancers Symposium, patients who had axitinib and prior lines actually did get responses with tivozanib. That is telling you that this is an active post-VEGF inhibitor. A lot of those patients had 2 TKIs prior to tivozanib. So why is it working?

There has been a lot of focus on different mechanisms of action, but we do not actually know what is going on in the tumor microenvironment of those individual patients. There are some patients who have a more angiogenic phenotype, and others more of an immunologic phenotype.

If there is resistance through either upregulation of VEGF receptors or changes in the VEGF receptor vs different types of resistance mechanisms, you may be better off with tivozanib if you need that extra VEGF punch. The problem is we do not know at any given time what that patient would be best served by. That is the challenge. But I would just highlight that it is not always about switching mechanisms of action. That is important, though, because if you must dose reduce, all the data about benefit start to get a little bit murkier as to how your individual patient is going to do in the clinic.

Are you giving them enough of a TKI to augment that anti-mTOR therapy? That is just something that I keep in mind when I am thinking about my patients and explaining choices of therapy.

REFERENCES

For more case-based articles and videos, scan the QR code or go to TargetedOnc.com/link/1535.
INDICATION AND USAGE
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

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
Effusion and Edema
Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%

Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression
Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions
Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.
Cutaneous Reactions (continued)
Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity
Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

ADVERSE REACTIONS
In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.
In LOTIS-2, serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.
Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.
Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.
Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to ADC Therapeutics at 1-855-690-0340.

Please see Brief Summary of the full Prescribing Information on adjacent pages.
INDICATIONS AND USAGE

ZYNLONTA® (loncastuximab tesirine-lpyl) for injection, for intravenous use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

INDICATIONS AND USAGE

ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. 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

Effusion and Edema. Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 4 or pericardial effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression. Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytophenia may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections. Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions. Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity. Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose (See Use in Specific Populations (8.1, 8.3)).

ADVERSE REACTIONS

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

Effusion and Edema

Myelosuppression

Infections

Cutaneous Reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADC-402-201 (LOTIS-2) and ADC-402-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles.

In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalimentinemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies [see Clinical Studies (14.1)]. The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory DLBCL who received ZYNLONTA in LOTIS-2.
Adverse reactions, including laboratory abnormalities, were thrombocytopenia, gastrointestinal disorders, myelosuppression, infections, and edema.

**PRECAUTIONS** reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.22 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and up to 8 cycles. A single dose of 0.4 mg/kg was 0.22 mg/kg.

Infections

**Myelosuppression**

- Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper
- Musculoskeletal pain includes musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, back pain, limb discomfort, myalgia, neck pain, non-cardiac chest pain, and pain in extremity
- Dyspnea includes dyspnea, and dyspnea exertional
- Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract congestion, nasopharyngitis, influenza,啼rhinus infection, and sinusitis

Clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA included:

- Blood and lymphatic system disorders: Febrile neutropenia (3%)
- Cardiac disorders: Pericardial effusion (3%)
- Infections: Pneumonia 3%, sepsis 2% (2%)
- Skin and subcutaneous disorders: Hyperpigmentation (4%)
- General disorders: Infusion site extravasation (1%)

**Pneumonia** includes pneumonia and lung infection

**Sepsis** includes sepsis, escherichia sepsis, and septic shock

**Selected Other Adverse Reactions**

- Inflammatory-related conditions were reported in 3% of patients in LOTIS-2, including pericarditis, pneumonitis, pleuritis, and dermatitis.

Table 2 summarizes the laboratory abnormalities in LOTIS-2.

### Table 2: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYNLONTAa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>58</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>52</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>51</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>57</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>48</td>
</tr>
<tr>
<td>AST increased</td>
<td>41</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
</tr>
<tr>
<td>ALT increased</td>
<td>34</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value.

*No Grade 4 adverse reactions occurred

**Immunogenicity**

As with all therapeutic proteins, there is 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 to loncastuximab tesirine-lyp in other studies or to other products may be misleading.

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine-lyp after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Data**

**Animal Data**

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-lyp. The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryo-toxicity and teratogenicity.

**Lactation**

**Risk Summary**

There is no data on the presence of loncastuximab tesirine-lyp or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

**Females and Males of Reproductive Potential**

ZYNLONTA can cause fetal harm when administered to pregnant women.

**Pregnancy Testing**

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

**Contraception**

Females: Advise women of reproductive potential to use effective contraception during treatment and for 9 months after the last dose.

**Males**

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 6 months after the last dose.

**Infertility**

Males: Based on the results from animal studies, ZYNLONTA may impair fertility in males. The effects were not reversible in male cynomolgus monkeys during the 12-week drug-free period.

**Pediatric Use**

Safety and effectiveness of ZYNLONTA in pediatric patients have not been established.

**Geriatric Use**

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

**Hepatic Impairment**

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN]) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).
Rizzieri Considers Prognostic Models and Trial Data for Myelofibrosis

**CASE**

- A 68-year-old woman presented to her physician with symptoms of fatigue and abdominal pain lasting 4 months. She also reported increased bruising and unexplained weight loss.
- Spleen was palpable 8 cm below the left costal margin.

**POLLING QUESTION**

During a live virtual event, Rizzieri asked participants, “What risk assessment tool do you use most often?”

- IPSS/DIPSS: 40% (4)
- DIPSS Plus: 40% (4)
- MIPSS70/MIPSS70 (V2.0): 10% (1)
- I do not use a formal risk assessment tool: 10% (1)
- Other: 0% (0)

Total votes: 10

**Targeted Oncology™: What baseline risk assessment models are available for myelofibrosis (MF)? How do they differ?**

**RIZZIERI:** The [prognostic models of MF] can differentiate the anticipated survival, which helps us understand when we might intervene with ruxolitinib [Jakafi], other approved therapies, or even transplant. These [models have undergone] evolution over time as we’ve understood more about the disease—from IPSS [International Prognostic Scoring System] to DIPSS [Dynamic IPSS] to DIPSS Plus.

The initial IPSS used easy, objective data. Currently, we like to add to that the karyotypic information when available.1,2 A lot of the patients with MF may not have that, but in patients [from whom] we can get this information, it improves prognostic abilities. There is also improvement with adding transfusion dependence, platelet count, etc.

The other aspect with DIPSS vs IPSS is that a time-dependent variable is built into DIPSS. Technically, IPSS would only be used at the time of diagnosis, but DIPSS can be used throughout the course of the patient’s illness. Whatever the patient’s score is when they’re seeing you in the office that day, you look at their survival from that point forward, not from the previous initial diagnosis. Prognostically, [this] is helpful when we’re thinking about other interventions.

The DIPSS and DIPPS Plus can help us in the low-, intermediate-, and high-risk groups to differentiate anticipated survival.3 The intermediate-2 and high-risk patients are those I would offer something potentially curative, such as allogeneic [transplant], if they’re a candidate and accepting of the risks. For those with lower risk, I would observe or treat them with other measures, depending on the circumstances.

**How does the MIPSS70 (Mutation-Enhanced IPSS 70) help assess patients?**

The MIPSS70 is really gaining ground. Of course, now we’re using MIPSS70-plus and 2.0 versions. Tefferi et al4 had a very similar, although slightly different, scale. The MIPSS70 had objective measures, such as counts in peripheral blasts, just like the DIPSS had. But then there is more importance to getting a bone marrow [test] and looking at the degree of fibrosis, [as well as] the gene analysis for the absence of a calreticulin type 1 [CALR] mutation. The [high-molecular risk] categories are those with highly mutated regions. Specifically in the MIPSS70, they are ASXL1, EZH2, SRSF2, and IDH1/2.4,5

Fluorescence in situ hybridization or molecular genetics can be helpful, because when you use this prognostic score, having 1 of these mutations is important in the ranking. If you have 2 or more, you have a higher risk ranking. The MIPSS70-plus adds in additional genetic information. This type of information is helpful because it differentiates the low-risk patients [who have a median overall survival (OS)
of 2.7 years vs the high-risk patients who have a median OS of 2.3 years.4

So, we can have an important discussion with the patient on where they fall in terms of expected changes in the illness and what that might mean for when we [would] intervene with potential therapi es. Our patient is high risk and they had at least 5 points [based on only bone marrow analysis], so I’m quite concerned about them progressing sooner rather than later, based on this model.

The MIPSS70-plus 2.0 incorporates further very high-risk karyotypes, and the U2AF1 Q157 mutation status, as well as sex, and defines 5 prognostic categories.6 Again, the very low-risk and low-risk patients do well, and depending on symptoms, we would look at those patients differently than the very high-risk and high-risk patients, [for whom] we may intervene differently.

How do other prognostic models and guidelines suggest managing a patient such as this?

There’s another available calculator for us to be aware of, which I find helpful—the MYSEC-PM [Myelofibrosis Secondary to PV and ET Prognostic Model]. This is a prognostic model specifically for patients with newly diagnosed post-PV [polycythemia vera] MF or post-ET [essential thrombocythemia] MF.7 These were the patients I saw a lot in a referral pattern when I was at Duke University Hospital doing transplants. Specialists in hematologic malignancies may see a skewed version of these patients, because after being ill for a long time, they get sent to [those] specialists. We typically would lump these patients as having secondary MF and being high risk, but that’s not the way they all are based on the MYSEC-PM.

Passamonti et al7 published a paper a few years ago, where they dissected high-risk and low-risk patients based on easy-to-obtain criteria, such as the standard objective hemogram blast, the genotype, and constitutional symptoms. The scores differentiated low-risk and high-risk groups. So in a patient with post-PV MF or post-ET MF, if they’re low risk, that’s a different conversation than the one about the high-risk or intermediate–2 risk patient who clearly has a different survival pattern. For our case patient, unfortunately, if they had post-PV or post-ET MF, they would have had a higher risk status, if that were the clinical scenario we were dealing with here.

The NCCN [National Comprehensive Cancer Network] guidelines are easily available to many of us.8 I find their guidance helpful. It doesn’t specify a specific right way to do things, because there’s more than 1 way to [treat]. The important thing is it gives us the arena we should be working in, and if we’re outside that arena, we’re probably doing something that’s not up-to-date. But if you’re within the NCCN guidelines, there’s an appropriate amount of variability, depending on your own practice pattern. So the MIPSS70, the DIPSS Plus, or the regular DIPSS can all be appropriately applied and can be reasonable in differentiating lower and higher risk. The stratum in those models can be helpful.

What therapy would you recommend for this patient?
Both ruxolitinib and fedratinib [Inrebic] are fair choices.

**FIGURE.** Patients With Spleen Volume Reduction of ≥ 35% in COMFORT-I and COMFORT-II9,10
She’s 68 years old, but if she has a robust [biological age] with nonablative therapy, certainly a referral for transplant to discuss risk and benefits is not unreasonable. But a majority of patients with MF don’t end up getting transplant for a variety of reasons.

Based on the NCCN guidelines, this patient would fall into the category of platelets more than 50 × 10^11/L. [She is] not a transplant candidate, which then leads to the 2 approved options [ruxolitinib and fedratinib]. The other options are if she was not a transplant candidate and had symptomatic anemia, which I don’t think she had, vs if she was a transplant candidate, [which], in that case, she would go for an allogeneic transplant consult.

Being a transplant candidate is tough. It depends on who’s seeing the patient. So if it’s unclear, it’s certainly worth a call to your transplant colleague to ask and at least have a consultation for many of these patients.

**Which data support the use of ruxolitinib for MF in the frontline setting?**

The data that informed some of the NCCN guidelines were based on the phase 3 COMFORT-I [NCT00952289] and COMFORT-II [NCT00934544] trials for ruxolitinib. COMFORT-I was a double-blind, placebo-controlled study for MF, with a 1:1 randomization. COMFORT-II used the best available therapy (BAT) instead of placebo, with a 2:1 randomization. 9,10

In both trials, patients had at least a 35% reduction in the spleen volume [Figure 9,10]. Many of these patients present with a large spleen, which is related to many of the other issues. This difference was important.

In COMFORT-I, 1 patient on placebo got a decrease in spleen volume because of an infarct, [which is] not what we like to see for our patients. But there’s a large portion of patients on ruxolitinib who overcame that 35% decrease. Even in those who didn’t meet the 35% decrease, a high proportion had some decrease in the splenic volume. 9

Again, the splenic volume in COMFORT-II showed a significant decrease, with a higher proportion receiving at least a 35% reduction. There were very few whose spleen size increased while on ruxolitinib. 10

COMFORT-I analyzed symptom response, which is a big aspect for a lot of our patients. We have the numbers and the physical exam findings, but how do the patients feel? They did exploratory analyses with the results published for the longer-term follow-up results. 9,10

There was a significant symptom reduction for ruxolitinib. What’s important is what specifically got better clinically. Abdominal discomfort and pain—of course, [because of reduced] splenomegaly—early satiety, night sweats, pruritus, muscle pains, and others in the symptom analysis trended to improvement with ruxolitinib. The COMFORT-II symptom response is a very similar story. 9,10

**How did patients do, in terms of efficacy end points, in the COMFORT trials?**

The OS data for the 2 studies were pooled, as they were not set up initially to look at that. There was crossover over time, which impacts survival, etc. But, with the benefit of time and following over 1000 patients, retrospectively, the COMFORT-I and COMFORT-II intent-to-treat groups had a median survival of [approximately] 70 months [95% CI, 61-76]. 11

The data suggest there may be an improvement with ruxolitinib therapy, which is interesting because for many of these patients, it was not ruxolitinib vs nothing, it was ruxolitinib vs the ability to cross over. So that’s an interesting thought. Some [final causes of death at final analysis] for patients were transformational leukemia, progression of MF, thrombosis, bleeding, infection, etc. 11

The splenic response was also noted to correlate with outcomes of ruxolitinib treatment. So the OS by spleen response at 6 months. Importantly, the durability of splenic response correlated with OS. 12

The efficacy by titrated dose from COMFORT-I is important when we’re working together with some of our colleagues on the phone, as we mentioned we don’t see this very often. It’s difficult to safely choose the right dose for many of these patients, as 25 mg twice a day may be too much for some. You don’t want to undertreat. We know [that for many patients], 5 mg twice a day is just not enough, but we don’t want to scare them away with treatment, either. So start with something low, make sure they tolerate it, get their trust that they’re not going to get too sick from it, and titrate up.

The key is starting low at 10 mg twice a day and escalating quickly to a maximum safe dose, because you’re going to know in a couple months whether the therapy works. You don’t want to undertreat at 5 mg twice a day for those 2 months. You [have] to be at a dose that can be effective, so at least 10 mg twice a day, titrating up appropriately to 15 mg, 20 mg, 25 mg. The splenic volume and total symptom score clearly improve in response when you’re at 10 mg twice a day or higher. 13

Hematologic grade 3 or 4 AEs [adverse events] include cytopenia, which is probably going to be worse than if they were on BAT or placebo. [Approximately] half the patients had worsening cytopenia, particularly anemia. 9,10

**Which other studies have looked at ruxolitinib in this patient population?**

[The EXPAND trial (NCT01317875)] had 2 strata based on platelet counts of patients: those with platelets between 75 and 99 × 10^11/L [n = 44] and those with platelets between 50 and 74 × 10^11/L [n = 25]. They started at 5 mg twice a day and escalated based on the cohorts that were proven to be safe. Both groups came to a recommended dosing of 10 mg twice a day to start, then escalate based on tolerance. 14,15
The EXPAND study final analysis looked at thrombocytopenia [and anemia in both groups]. The data suggest cytopenia are going to be common—something we must manage through. In patients with platelet counts of 50 to 100 × 10^9/L—even though we were starting at 10 mg twice a day and escalating up—if you can keep these patients on therapy, they still have a very high chance of a splenic response. Then with that, the chance in symptom score in both strata, as well.

Which data support the use of fedratinib for MF in the frontline setting?
The JAKARTA study [NCT01437787] is the study that primarily led to the approval of fedratinib in patients with intermediate-2 or high-risk MF. There are lots of data now supporting this approved agent. The randomization was 1:1 for fedratinib at 400 mg or 500 mg a day vs placebo, and 96 patients were randomized to each arm.

The response by platelet count was interesting. [The group with platelet counts of under 100 × 10^9/L had a spleen response of 36%, and those with over 100 × 10^9/L had a response of 49%] that is a clinically significant number in this small group of patients. There is a trend, but again, I don’t know that it’s real. It was similar with symptom response, with those with platelet counts under 100 × 10^9/L having a response of 31%, and those with over 100 × 10^9/L platelets having a response of 42%. There are AEs to be aware of, particularly the GI [gastrointestinal] ones with fedratinib. Approximately 50% to two-thirds of patients had some GI effects with fedratinib, but the grade 3 and 4 GI AEs were not so significant. The anemia was 30% for grade 3 and 4 in the fedratinib group and 10% in the placebo group. In addition, the laboratory abnormalities, including hemogram changes, were in both groups, but maybe slightly more accentuated in fedratinib compared with placebo in this regard.

The one concern that might be different in the JAKARTA study was the black box warning that came out of the study was the black box warning that came out of the phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis. The randomization was 1:1 for fedratinib at 400 mg or 500 mg a day vs placebo, and 96 patients were randomized to each arm.

The response by platelet count was interesting. [The group with platelet counts of under 100 × 10^9/L had a spleen response of 36%, and those with over 100 × 10^9/L had a response of 49%] that is a clinically significant number in this small group of patients. There is a trend, but again, I don’t know that it’s real. It was similar with symptom response, with those with platelet counts under 100 × 10^9/L having a response of 31%, and those with over 100 × 10^9/L platelets having a response of 42%. There are AEs to be aware of, particularly the GI [gastrointestinal] ones with fedratinib. Approximately 50% to two-thirds of patients had some GI effects with fedratinib, but the grade 3 and 4 GI AEs were not so significant. The anemia was 30% for grade 3 and 4 in the fedratinib group and 10% in the placebo group. In addition, the laboratory abnormalities, including hemogram changes, were in both groups, but maybe slightly more accentuated in fedratinib compared with placebo in this regard.

The one concern that might be different in the JAKARTA study was the black box warning that came out of the data for the serious and fatal encephalopathy, including Werneric encephalopathy and encephalopathy of unclear origin.

REFERENCES

15. Guglielmelli P, Kiladjian JJ, Vannucchi AM, et al. The final analysis of EXPAND: a phase 1b, open-label, dose-finding study of ruxolitinib (RUX) in patients (pts) with myelofibrosis (MF) and low platelet (PLT) count (50 × 10^9/L to < 100 × 10^9/L) at baseline. Blood. 2020;136(suppl 1):e4-5. doi.org/10.1182/blood-2020-137742
For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

**A WAY IN WITH TRODELVY**

TRODELVY attacks mTNBC with an antibody-drug conjugate (ADC) that binds to Trop-2.¹

Based on preclinical data. May not correlate with clinical outcomes.

**INDICATION**

TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNING: NEUTROPENIA AND DIARRHEA**

- Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.
- Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.

**CONTRAINDICATIONS**

- Severe hypersensitivity reaction to TRODELVY.

**WARNINGS AND PRECAUTIONS**

**Neutropenia:** Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

**Diarrhea:** Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.3% of patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can receive appropriate premedication (e.g., atropine) for subsequent treatments.

**Hypersensitivity and Infusion-Related Reactions:** Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 17% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Pre-infusion medication is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

©2021 Gilead Sciences, Inc. All rights reserved. 2021-US-TROT-00040 05/21

GILEAD, TRODELVY, and the GILEAD and TRODELVY logos are trademarks of Gilead Sciences, Inc.
For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

**TRODELVY IMPROVED SURVIVAL IN 2L+ mTNBC**

In the phase 3 ASCENT trial*

**PROVEN SURVIVAL BENEFIT**

<table>
<thead>
<tr>
<th>Population</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>In brain metastases-negative (BM-neg) population**</td>
<td>5.6 months with TRODELVY (range: 4.3–6.8) (n=233) vs 1.7 months with single-agent chemotherapy (range: 1.5–2.8) (n=233); 95% CI, HR: 0.41 (0.32–0.52) P&lt;.0001</td>
<td>12.1 months with TRODELVY (range: 10.7–14.0) (n=235) vs 6.7 months with single-agent chemotherapy (range: 5.8–7.7) (n=233); 93% CI, HR: 0.48 (0.38–0.59) P&lt;.0001</td>
</tr>
<tr>
<td>In the full population*</td>
<td>Median PFS was 4.8 months for TRODELVY (range: 4.1–5.8) (n=267) vs 1.7 months with single-agent chemotherapy (range: 1.5–2.5) (n=262); 95% CI, HR: 0.43 (0.35–0.54) P&lt;.0001</td>
<td>11.8 months with TRODELVY (range: 10.5–13.8) (n=267) vs 6.9 months with single-agent chemotherapy (range: 5.9–7.6) (n=262); 95% CI, HR: 0.51 (0.41–0.62) P&lt;.0001</td>
</tr>
</tbody>
</table>

*TRODELVY was studied in ASCENT, a phase 3, randomized, active-controlled, open-label trial. Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=267) or physician’s choice of single-agent chemotherapy (n=262), which included eribulin, vinorelbine, gemcitabine, or capetitabine. Patients were treated until disease progression or unacceptable toxicity. The efficacy analysis included Progression-Free Survival (PFS) in BM-neg patients (primary endpoint) by BICR based on RECIST 1.1 criteria, PFS for the full population (all patients with and without brain metastases), and Overall Survival (OS) vs single-agent chemotherapy.

**Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity:** Patients homozygous for the uridine diphosphate–glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of Grade 3–4 neutropenia was 67% in patients homozygous for the UGT1A1*28 allele and 46% in patients heterozygous for the UGT1A1*28 allele and 67% in patients homozygous for the wild-type allele. The incidence of Grade 3–4 neutropenia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 function.

**Embryo-Fetal Toxicity:** Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. 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 TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

**ADVERSE REACTIONS**

**In the ASCENT study (IMMU-132-05),** the most common adverse reactions (incidence ≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3–4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

**DRUG INTERACTIONS**

**UGT1A1 Inhibitors:** Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

**UGT1A1 Inducers:** Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.


Please see Brief Summary of Full Prescribing Information, including BOXED WARNING, on the next page.
**WARNING: NEUTROPENIA AND DIARRHEA**

Severe neutropenia, defined as Grade 4 neutropenia (ANC ≤ 500/mm^3), can occur during treatment with TRODELVY.

Severe diarrhea occurs in 0.5% of patients. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment.

**Severe hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of treatment.**

**Diarrhea:**

Toxicity, defined as Grade 4 non-neutropenic hematologic or non-hematologic toxicity, persisting >48 hours despite optimal medical management, OR at time of scheduled treatment, Grade 3-4 neutropenia which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1.

At first occurrence, 25% dose reduction. At second occurrence, 25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF). At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY.

At time of scheduled treatment, Grade 3-4 neutropenia occurs which delays dosing beyond 3 weeks for recovery to ≤ Grade 1, discontinue TRODELVY at first occurrence.

**Severe Non-Neutropenic Toxicity**

Defined as Grade 4 non-neutropenic hematoxylin or any duration, OR any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents, OR other Grade 3-4 non-neutropenic hematologic toxicity persisting >48 hours despite optimal medical management, OR at time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1.

At first occurrence, 25% dose reduction. At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY.

In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks, discontinue TRODELVY at first occurrence.

**CONTAINING AREAS**

**Also see Warnings and Precautions**

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

**WARNING AND PRECAUTIONS**

**Also see BOXED WARNING, Dosage and Administration, Contraindications, Clinical Pharmacology, Nonclinical Toxicology, and Use in Specific Populations**

**Neutropenia:** Severe neutropenia (ANC < 500/mm^3) can occur in patients treated with TRODELVY.

Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7% of patients. Withhold TRODELVY for ANC below 1500/mm

**Embryo-Fetal Toxicity:**

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose. Advise male partners of female partners with reproductive potential to use effective contraception during treatment with TRODELVY

**DOSAGE AND ADMINISTRATION**

**Also see Warnings and Precautions**

Do NOT substitute TRODELVY for or with other drugs containing rituximab or its active metabolite 38-IA.

The recommended dose of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of a 21-day treatment cycle. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg. Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 10 minutes following the initial dose, for signs or symptoms of infusion-related reactions.

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and at least 1 hour after infusion.

Pretreatment: Prior to each dose of TRODELVY, pretreatment for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended. Pretreatment with antihistamines, H1 and H2 blockers prior to infusion is recommended for patients who have prior history of infusion reactions.

Pretreatment with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist, as well as other drugs as indicated).

**Dose Modifications for Infusion-related Reactions:**

Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions.

Dose Modifications for Adverse Reactions: Withhold or discontinue TRODELVY to manage adverse reactions as described below. Do not re-evaluate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Severe neutropenia, defined as Grade 4 neutropenia ≥28 days, Grade 3-4 absolute neutrophil count or ANC < 1000/mm

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

TRODELVY is a registered trademark of Gilead Sciences, Inc.

© 2021 Gilead Sciences, Inc. All rights reserved. 2021-US-TROT-00040 05/21
Clinical Commentary: Addressing Challenges in Unresectable HCC and Adding Lenvatinib to Therapy Sequencing

EVENT SUMMARY
At a live virtual event, Ghassan K. Abou-Alfa, MD, discussed therapeutic sequencing for patients with unresectable hepatocellular carcinoma (HCC) and concerns with serious adverse events (AEs) that are seen in multiple treatments for this patient population. Abou-Alfa also detailed the benefits of lenvatinib (Lenvima) in this patient population over sorafenib (Nexavar) and how he would use lenvatinib in the second-line setting of treatment as well.

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

Serious AE Concerns in Certain Treatments
Interestingly, I would say that the concern about Crohn’s disease with infliximab [Remicade], and regarding checkpoint inhibitors, is valid.¹ Maybe it’s not an absolute, but it’s valid, and if you decide to do that, you usually will send the patient to a gastroenterologist so that they assess the patient. They’ll tell you what kind of stability the patient has so you can get some sense about what you’re concerned about and if [you should stay] concerned about it. When it comes to the variceal bleeding [seen in patients], I would be more seriously concerned and even push [addressing it] further.²

Six months is at least my minimum regarding variceal bleeding to be banded without any activity because you can pull it out. As you can imagine, the variceal bleeding is like very high-pressure vessels that when they open in the esophagus they pour blood like there’s no tomorrow. I’m sure some of you might have the sad reality of seeing one of those gastrointestinal [GI] bleeds coming out of variceal bleeding in the emergency room. They are not a joke. I would say this is where I would not fiddle at all. If a patient had, 2 months ago, a variceal bleed, I would not give bevacizumab [Avastin].

Now, when sorafenib came on board, the sponsor tried to push for lower doses with the idea that maybe there would be less hand-foot syndrome. But I would say that starting at 12 mg, with the understanding that we can lower it if need be, is totally OK [Table 4].

The most important thing, regardless, is to make sure that you see those patients. When I start somebody on lenvatinib or sorafenib, I’ll see them within a week because you have to keep an eye on them because things will declare themselves very quickly and you’ll be able to decide then if you need that break to bring the dose down. I would say 12 mg has been the standard, and I would not make shortcuts on this because we might not necessarily benefit the patient. Moreover, I would say the combination of atezolizumab and bevacizumab, in that case, is probably not the right answer.

Lenvatinib or sorafenib are appropriate. Oxaliplatin, fluorouracil, and folinic acid [FOLFOX], interestingly, is a standard of care, but not in the United States, whereas in China it’s an appropriate first-line therapy.⁴ Nivolumab [Opdivo] was also pulled out of the market for that purpose.⁵ It did not benefit patients because the study was negative, and I would not bring the nivolumab as a standard of care. The guidelines from the National Comprehensive Cancer Network [NCCN] classify atezolizumab/bevacizumab as A1, sorafenib as A1 or B7, and lenvatinib as A1.
Interestingly, they are still kind of chatting about nivolumab because they have it for Child-Pugh B, but I don’t know, the NCCN is going to probably revise it because the drug is not yet approved and the request for approval was pulled out. FOLFOX was kind of determined as an option simply because of the data that came out for the FOLFOX regimen when they compared it with doxorubicin a long time ago.

The question [when looking at these various options is]: How can we get a little bit of a better read on this? Of course, more data, better data, improved outcomes are needed, but that’s the beauty of us talking to each other [at live events like the Case-Based Roundtable Series], that we learn from each other what could be the important variables that can decide one way or the other.

### Systemic Therapy vs Interventional Radiology Therapy

Historically, the interventional radiology people have been heavily involved because, humbly and sadly, we did not have options. But now we are loaded with options, and if anything, patients know about the options, and they want to get a [better treatment] opportunity from them.

So the best data we have come from Japan where if the disease is limited to the liver, because remember if it’s metastatic then it’s systemic therapy for sure, but if it’s limited to the liver and the number of lesions is counted [patients may be better candidates for systemic therapy].

Let’s say, for argument’s sake, there are 4 lesions in the liver and if you add the size of the largest lesion, which, let’s say, is 4 cm, is equal to 8 [lesions]. [The researchers from Japan then] found out that patients who have more than 7 points, what they call up to 7 criteria based on transplant data, patients will not do very well on the local therapy. Therefore, it would be recommended to do systemic therapy.

In their trial, they randomized patients with up to 7 criteria with only locally advanced disease in the liver, and they randomized them to embolizations, same way that one would see patients do vs lenvatinib.

The median survival for the embolization was at 20 months and that’s exactly what has been reported by a couple of groups—interestingly, for the patients on lenvatinib, for local therapy for 58 months, which I think tells us something. So I would say [to other clinicians in this situation to] please make sure if you have a tumor board, and if you have access to your tumor board, to always be there to make sure you are heard. The data are there, and one can definitely stand in a meeting and say [that if there are more than 7 criteria determined like on this study], then I think it’s time to use systemic therapy.

### REFLECT TRIAL

The open-label, phase 3, multicenter noninferiority trial [NCT01761266] recruited patients with unresectable hepatocellular carcinoma, who had not received treatment for advanced disease, at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American regions. Patients were randomized 1:1 to receive either 12 mg/day of oral lenvatinib or 400 mg of sorafenib twice daily in 28-daily cycles. The primary end point of the study was overall survival (OS), measured from the date of randomization until the date of death from any cause, and an efficacy analysis followed the intention to treat principle.

### Data Backing the Choice of Lenvatinib

[The first kind of complex results comparing these 2 drugs came] from the REFLECT trial. The study was positive because it looked at noninferiority and there was no inferiority observed. Interestingly, it showed a new median OS of 13.6 months for patients on lenvatinib compared with 12.3 months for patients on sorafenib, with a hazard ratio of 0.92 (95% CI, 0.79-1.06).

Now, we know that lenvatinib has an anti-EGFR activity that is very robust, and that activity is about 80 times higher than sorafenib. That’s why we use only 12 mg of lenvatinib while we use 800 mg of sorafenib. Interestingly, this reflected on the progression-free survival [PFS], which was almost close to 3 times higher for patients on lenvatinib at [a median of 7.4 months vs 3.7 months (HR 0.66; 95% CI, 0.57-0.77; \( P<.0001 \)]). So [if you think

### TABLE. Lenvatinib AE Monitoring and Dose Reduction Recommendations

<table>
<thead>
<tr>
<th>PATIENT WEIGHT</th>
<th>STARTING DOSE</th>
<th>FIRST DOSAGE REDUCTION</th>
<th>SECOND DOSAGE REDUCTION</th>
<th>THIRD DOSAGE REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>8 mg every day</td>
<td>4 mg every day</td>
<td>4 mg every 2 days</td>
<td>Discontinue</td>
</tr>
<tr>
<td>&gt; 60 kg</td>
<td>12 mg every day</td>
<td>8 mg every day</td>
<td>4 mg every day</td>
<td>4 mg every 2 days</td>
</tr>
</tbody>
</table>

**HEPATOCELLULAR CARCINOMA**

**TABLE. Lenvatinib AE Monitoring and Dose Reduction Recommendations**

<table>
<thead>
<tr>
<th>PATIENT WEIGHT</th>
<th>STARTING DOSE</th>
<th>FIRST DOSAGE REDUCTION</th>
<th>SECOND DOSAGE REDUCTION</th>
<th>THIRD DOSAGE REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>8 mg every day</td>
<td>4 mg every day</td>
<td>4 mg every 2 days</td>
<td>Discontinue</td>
</tr>
<tr>
<td>&gt; 60 kg</td>
<td>12 mg every day</td>
<td>8 mg every day</td>
<td>4 mg every day</td>
<td>4 mg every 2 days</td>
</tr>
</tbody>
</table>
about it like you have a racetrack, which is exactly 1 length, it does not mean you cannot have a faster car, and that’s where the faster car of the lenvatinib comes into play for this disease.

Second-Line Therapy After Disease Progression
I personally stand by still using lenvatinib [in this setting] because we’re not going to discredit the first-line therapy, like lenvatinib, sorafenib, and of course, if anybody progresses on atezolizumab plus bevacizumab, it’s still not a bad idea to get them to the lenvatinib as second line.

When looking again at the NCCN guidelines, it’s amazing that they said subsequent-line therapy in this disease progression does include lenvatinib and sorafenib. Interestingly, I notice that there’s a lot of complexity with too many drugs coming very quickly, enough that it might not even catch up with first and second line.

I understand that people might be concerned about the safety and tolerability [of the drug] in the second line, but I could assure [people with those concerns that] in the old days, maybe 15 years ago, if you asked me about the second line, I’d tell you I’m not sure that patients will do well. We have also come out with great therapies these days and people do very well. So don’t discredit that the patient might do very well in that regard. If anything, in the second line, the options for therapy include lenvatinib, cabozantinib, and sorafenib, and I know many that would choose lenvatinib, which is my default [in this setting] as well.

REFERENCES

How Goals Help Determine Frontline Treatment in HCC
Michael A. Morse, MD, FACP, discusses the challenges of treating patients with hepatocellular carcinoma and how setting the right goals for patient care can make a difference in the treatment plan.
Khan Reviews Later-Line Therapy Options for DLBCL With Subgroup Considerations

### CASE

- A 79-year-old man presented with fever, a 7-lb unintentional weight loss, and occasional chest pain.
- Medical history: hypertension, medically controlled; cardiac failure; atrial fibrillation
- Physical exam: appeared tired; palpable bilateral cervical lymphadenopathy
- Laboratory results:
  - Lactate dehydrogenase: 300 U/L
  - Hemoglobin: 10.8 g/dL
  - Bilirubin: 1.3 mg/dL
  - Creatinine: 1.7 mg/dL
- All other values: within normal limits
- HIV/hepatitis B/C: negative
- Lymph node biopsy:
  - Immunohistochemistry panel: CD10+ and CD20+ confirmed diffuse large B-cell lymphoma (DLBCL)
  - Fluorescence in situ hybridization: negative for rearrangements of BCL6, BCL2, and MYC
- Imaging studies:
  - Whole-body positron emission tomography (PET)/CT scan showed activity in multiple lymph nodes above and below the diaphragm (largest node, 3.9 cm) and evidence of subcutaneous tissue involvement.
  - MRI of the brain showed no evidence of lesions.
- Staging: stage IV; International Prognostic Index (IPI), high risk; Ann Arbor stage III/IV
- ECOG performance status: 1
- The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone), which was well tolerated.
- PET scan at the end of treatment showed complete remission.
- One year later, the patient presented with diffuse lymphadenopathy, confirmed by PET/CT scan.
- Biopsy showed relapse of DLBCL.
- The patient was considered ineligible for transplant due to older age and high risk.
- The patient received second-line GemOx (gemcitabine and oxaliplatin) plus rituximab, with a partial response (PR).
- Overt disease progression 5 months later

---

**Targeted Oncology™**: What are the treatment options for patients with relapsed DLBCL?

**KHAN**: The treatment options for these patients have expanded a lot over the last few years and gladly so. We’ve needed a lot of novel agents and treatments for patients, particularly in the older population and for high-risk patients.

According to the current NCCN [National Comprehensive Cancer Network] guidelines, second-line therapies for patients who are transplant eligible include a few salvage regimens. The most commonly used is R-ICE [ifosfamide, carboplatin, and etoposide ± rituximab], followed by GDP [gemcitabine, dexamethasone, and cisplatin or carboplatin ± rituximab] and DHAP [dexamethasone, cytarabine + carboplatin, cisplatin, or oxaliplatin ± rituximab]. Other recommended regimens are ESHAP [etoposide, methylprednisolone, cytarabine, and cisplatin ± rituximab], GemOx, and MINE [mesna, ifosfamide, mitoxantrone, and etoposide ± rituximab].

Then of course for patients who are not transplant candidates, the preferred regimens include GemOx plus rituximab, pola-BR [polatuzumab vedotin-piiq (Polivy) with bendamustine (Treanda) and rituximab], and tafasitamab-cxix [Monjuvi] plus lenalidomide [Revlimid]. There are a few other recommended regimens as well. Finally, there are some regimens that are not FDA approved yet but can be useful in certain circumstances. For example, ibrutinib [Imbruvica] and R2 [lenalidomide and rituximab] are recommended for non-GCB [germinal center B-cell–like] DLBCL subtypes, and brentuximab vedotin [Adcetris] can be used for CD30-positive disease.
For CAR [chimeric antigen receptor] T-cell therapy regimens, it is important to control the disease a bit before collecting the MNCs [mononuclear cells]. Then there are a few options including GDP, ICE, GemOx, and pola-BR.\(^1\)

Typically what we’ve done as a bridge therapy is pola alone because we know bendamustine is T-cell depleting, so you might have some problems during collection with pola-BR. GemOx is also a common bridging regimen. For eligible patients, an allogeneic hematopoietic cell transplant may be considered as consolidation post second-line therapy,\(^1\) and pretty tough disease control is needed.

There’s not a great graft-vs-lymphoma effect in DLBCL, so not an easy process for those patients. Then for third-line and subsequent therapy, we have 3 approved anti-CD19 CAR T-cell therapies: axi-cel [axicabtagene ciloleucel (Yescarta)], lisocabtagene maraleucel [Breyanzi], and tisagenlecleucel [Kymriah]. Loncastuximab tesirine [lonca (Zynlonta)], a monoclonal antibody-drug conjugate targeting CD19, is also an option, as well as selinexor [Xpovio], a selective nuclear export blocker.\(^1\)

**POLLING QUESTION**

During a live virtual event, Khan asked participants, “What would you most likely recommend for this patient now, after chemoinmunotherapy?”

- Polatuzumab vedotin ± bendamustine/rituximab 42% (5)
- Tafasitamab/lenalidomide 33% (4)
- Rituximab-based chemotherapy 17% (2)
- Loncastuximab tesirine 8% (1)
- Other/clinical trial 0% (0)

Total votes: 12

During a live virtual event, Khan asked participants, “What would you most likely recommend for this patient now, after chemoinmunotherapy?”

What data support the use of these options for patients with DLBCL after chemoinmunotherapy?

There are multiple studies investigating this question. For example, the phase 2 pola-BR study [NCT02257567] included a phase 1b safety run-in \([n = 6]\), followed by randomized cohorts—pola-BR \([n = 40]\) vs BR \([n = 40]\)—and a single-arm pola-BR extension \((n = 106)\) cohort for patients with relapsed or refractory \([R/R]\) DLBCL. The idea was to investigate whether pola-BR worked together and whether the combination was toxic.\(^2,3\)

An important point to note is that we have so many different novel agent combinations. Not all of them are equal and unfortunately none of them have been compared to each other, so we can’t compare across trials. On the other hand, at least whenever you have a patient, you can put them on a treatment that probably was reflected in one of the latest clinical trials.

Adult patients, aged 18 years or older, with biopsy-confirmed R/R DLBCL and an ECOG performance status score between 0 and 2 had to be transplant ineligible or have had treatment failure with prior transplant and have received at least 1 prior line of therapy to meet the inclusion criteria for this study.\(^2,3\) However, if patients underwent a prior allogeneic stem cell transplant, an autologous stem cell transplant within 100 days prior to cycle 1 day 1, had a history of transformed disease, grade 1 or higher peripheral neuropathy, or were eligible for an autologous transplant, then they were excluded from this study.

Pola-BR given is every 21 days for 6 cycles only. The polatuzumab dose is 1.8 mg/kg, and is given on day 1; the bendamustine dose is 90 mg/m\(^2\) given by intravenous [IV] infusion on days 1 and 2, and the rituximab dose was the standard [375 mg/m\(^2\) on day 1 of each cycle].\(^2,3\)

Remember that in all other lymphomas, we generally give BR every 28 days, however, in DLBCL the dosing is every 21 days. Polatuzumab is an antibody-drug conjugate against CD79B,\(^2,3\) and the active chemotherapy is monomethyl auristatin E, the same regimen used in brentuximab vedotin.

In the pooled data analysis \([n = 152]\), the median age was 69 years, with a range of 24 to 94 years. Almost all patients had high-stage disease, with a median of 2 prior lines of therapy [range, 1-7]. There was an even distribution of percentage of patients with 1, 2, or [greater than or equal to] 3 prior lines of therapy. Most of the patients had a quick relapse [with duration of response (DOR) to their last treatment 12 months or less], and a lot of them were refractory to the last prior therapy. Some patients [18\%] had a prior transplant, and 39\% had a germinal center subtype. The median time to first response was 2 months [range, 1.8-5.3].\(^2,3\) This is sort of reflective of what we see in our clinics.

The independent review committee [IRC] assessed objective response in the randomized arm was 45\% in the pola-BR cohort vs 17.5\% in the BR cohort. So based on these results, naturally polatuzumab was added in the extension arm, which had an IRC overall response rate [ORR] of 41.5\%, including complete responses [CRs] and PRs.\(^2,3\)

The median IRC DOR was similar for the randomized and extension cohorts, at 10.9 months for the pola-BR arm, 10.6 [months] for the BR arm, and 9.5 months for the extension cohort. The median progression-free survival [PFS] was 9.2 months for pola-BR, only 3.7 months for BR, and 6.6 months for the extension cohort. The median follow-up was 48.9 months for pola-BR, 48.3 months for BR, and 15.2 months for the extension cohort.\(^3\)

continued on page 106
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

**ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE**

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial

**IMPORTANT SAFETY INFORMATION**

**DARZALEX® AND DARZALEX FASPRO®:**

**CONTRAINDICATIONS**

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

**DARZALEX®: Infusion-Related Reactions**

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours).

Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, i.e., 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute...
Powerful efficacy to start the treatment journey\(^1,4\)

After a median ~30 months\(^*\) of follow-up, mPFS was not reached with DARZALEX® + Rd vs 31.9 months with Rd alone.\(^1,4\)

- 70.6% of patients had not progressed with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)\(^1\)
- **44% reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.56; 95% CI, 0.43–0.73; P<0.0001)

Demonstrated safety profile (median treatment duration of 25.3 months)\(^1\)

- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.\(^1\)

At median ~5 years of follow-up\(^2,3\):

- **Efficacy results in long-term follow-up\(^2,3\)**
  - At median ~5 years (56 months)\(^2\) of follow-up, mPFS was not reached with DRd vs 34.4 months with Rd alone.\(^2\)
  - 53% of patients had not progressed after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35)\(^1\)
  - **47% reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

Safety results in long-term follow-up (median treatment duration of 47.5 months)\(^2\)

- With an ~3 to 5 minute subcutaneous injection, DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.\(^{5,11}\)

### Important Safety Information

- **Powerful efficacy to start the treatment journey**
- **Demonstrated safety profile** (median treatment duration of 25.3 months)
- **MAIA Study Design**
- **Efficacy results in long-term follow-up**
- **Safety results in long-term follow-up**

---

appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

**DARZALEX FASPRO®: 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®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

**Systemic Reactions**

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. 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, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetylsalicylic acid, 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 **IMMEDIATE MEDICAL CARE.**

---

\(^1\) Kaplan-Meier estimate.

\(^2\) TEAE=treatment-emergent adverse event.

\(^3\) Safety results in long-term follow-up.

\(^4\) CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); Rd=lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRR=injection-related reaction; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d). TEAE=treatment-emergent adverse event.

\(^5\) Range: 0.03-69.52 months. 3

\(^6\) CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); Rd=lenalidomide (R) + dexamethasone (d). TEAE=treatment-emergent adverse event.

\(^7\) Kaplan-Meier estimate.

\(^8\) Range: 0.0-41.4 months. 4

\(^9\) Powerful efficacy to start the treatment journey

\(^3\) Safety results in long-term follow-up

\(^4\) Efficacy results in long-term follow-up

\(^1\) At median ~5 years of follow-up

\(^2\) Safety results in long-term follow-up

\(^3\) With an ~3 to 5 minute subcutaneous injection

\(^4\) Efficacy results in long-term follow-up

\(^1\) Safety results in long-term follow-up

\(^2\) At median ~5 years of follow-up

\(^3\) MAIA Study Design

\(^4\) Important Safety Information

---

With an ~3 to 5 minute subcutaneous injection, DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.\(^{5,11}\)

See the latest data rolling out. Visit FrontlineMomentum.com
Based on the mechanism of action, DARZALEX® and DARZALEX® can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein. This interference can impact the determination of endogenous M-protein. Daratumumab is a human immunoglobulin G (IgG) kappa antigen in the patient's serum. The determination of a patient's ABO antigens in the patient's serum. Daratumumab-mediated positive indirect antiglobulin test may cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX® can cause fetal harm when administered to a pregnant woman. Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab mediates positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab has been shown to be effective in patients who have been transfused with DARZALEX® or DARZALEX® for a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX®. Monitor for local reactions and consider symptomatic management.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (≥1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 1 minute to 6.5 days) after starting administration of DARZALEX®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX®: Neutropenia and Thrombocytopenia
Daratumumab and Daruratumab can cause thrombocytopenia and thrombocytopenia induced by background therapy. 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® or DARZALEX® until recovery of neutrophils or for recovery of platelets. Daratumumab and DARZALEX® may increase neutrophilia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies.

DARZALEX® and DARZALEX®: Interference With Determination of Complete Response
Daratumumab is a human immunoglobulin G (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 patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX®: Embryofetal Toxicity
Based on the mechanism of action, DARZALEX® and DARZALEX® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX® may cause delay of fetal immune development and decreased bone density. Advise pregnancy women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX® for 3 months after the last dose.

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

DARZALEX®: Adverse Reactions
In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS
DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:
- 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, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX® (daratumumab and hyaluronidase-fihj) 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, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of 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 PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Please see Brief Summary of full prescribing information for DARZALEX® and DARZALEX® on adjacent pages.


© Janssen Biotech, Inc. 2022
All rights reserved.
**Indications and Usage**

DARZALEX® is indicated for the treatment of adult patients with multiple myeloma:

- 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.

**Contraindications**

DARZALEX® is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation [see Warnings and Precautions].

**Warnings and Precautions**

**Infusion-Related Reactions**

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported [see Adverse Reactions].

In clinical trials (monotherapy and combination: N=2,060), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision [see Adverse Reactions].

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was 16 mg/kg, the same used for the last DARZALEX® infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4:<1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 38%, with 38% of patients experiencing infusion-related reactions on Day 1 and 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 2.4 hours for the subsequent infusions.

Pre-mEDIATE patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion [see Dosage and Administration (2.3) in Full Prescribing Information]. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion [see Dosage and Administration (2.4) in Full Prescribing Information].

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions [see Dosage and Administration (2.3) in Full Prescribing Information]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease [see Dosage and Administration (2.3) in Full Prescribing Information].

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

**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 infusion. 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].

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX® [see Dosage and Administration (2.1) in Full Prescribing Information].

**Neutropenia**

DARZALEX® 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® until recovery of neutrophils.

**Thrombocytopenia**

DARZALEX® 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® until recovery of platelets.

**Interference with Determination of Complete Response**

Daratumumab is a human IgG kappa monoclonal antibody that can be detected in 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 patients with IgG kappa myeloma protein.

**Embryo-Fetal Toxicity**

Based on the mechanism of action, DARZALEX® can cause fetal harm when administered to a pregnant woman. DARZALEX® may cause death 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® and for 3 months after the last dose [see Use in Specific Populations].

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

**Adverse Reactions**

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

- Infusion-related reactions [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

**Clinical Trials Experience**

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

The safety data described below reflects exposure to DARZALEX® (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX® in combination with background regimens and 156 patients who received DARZALEX® as monotherapy. In this pooled safety population, the most common adverse reactions (≥25%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

**Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant**

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX® in combination with lenalidomide and dexamethasone was evaluated in MAIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 1 reflect exposure to DARZALEX® for a median treatment duration of 25.3 months (range: 0.1 to 40.64 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd). Serious adverse reactions with a 2% greater incidence in the RDd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).
### Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>0</td>
<td>46</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>41</td>
<td>1</td>
<td>&lt;1</td>
<td>36</td>
<td>&lt;1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>&lt;1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>Upper respiratory tract infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52</td>
<td>2</td>
<td>&lt;1</td>
<td>36</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29</td>
<td>3</td>
<td>0</td>
<td>21</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>26</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Infusion-related reactions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>41</td>
<td>2</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral edema&lt;sup&gt;e&lt;/sup&gt;</td>
<td>41</td>
<td>2</td>
<td>0</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
<td>0</td>
<td>28</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>3</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
<td>0</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>13</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Back pain</td>
<td>34</td>
<td>3</td>
<td>&lt;1</td>
<td>26</td>
<td>3</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>29</td>
<td>1</td>
<td>0</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Dyspnea&lt;sup&gt;f&lt;/sup&gt;</td>
<td>52</td>
<td>3</td>
<td>&lt;1</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough&lt;sup&gt;g&lt;/sup&gt;</td>
<td>30</td>
<td>&lt;1</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>14</td>
<td>1</td>
<td>&lt;1</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hypertension&lt;sup&gt;h&lt;/sup&gt;</td>
<td>13</td>
<td>6</td>
<td>&lt;1</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

<sup>a</sup> Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Orfhegynale candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

<sup>b</sup> Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

<sup>c</sup> Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

<sup>d</sup> Infusion-related reaction includes terms determined by investigators to be related to infusion

<sup>e</sup> Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling

<sup>f</sup> Cough, Productive cough

<sup>g</sup> Blood pressure increased, Hypertension

### Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhea</td>
<td>90</td>
<td>5</td>
<td>0</td>
<td>82</td>
<td>20</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
<td>17</td>
<td>77</td>
<td>28</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>84</td>
<td>41</td>
<td>11</td>
<td>75</td>
<td>36</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
<td>3</td>
<td>58</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>47</td>
<td>13</td>
<td>0</td>
<td>57</td>
<td>24</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

### Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td>Upper respiratory tract infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>6</td>
<td>&lt;1</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Infusion-related reactions&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>35</td>
<td>6</td>
<td>&lt;1</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
<td>0</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Cough&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspnea&lt;sup&gt;d&lt;/sup&gt;</td>
<td>21</td>
<td>3</td>
<td>&lt;1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Muscle spasms</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>2</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

<sup>a</sup> upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

<sup>b</sup> Infusion-related reaction includes terms determined by investigators to be related to infusion

<sup>c</sup> cough, productive cough, allergic cough

<sup>d</sup> dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.
Grade 3 or 4 infections were reported as follows: herpes zoster was reported in 2-5% of patients receiving DARZALEX. Prophylaxis for Herpes Zoster Virus reactivation was recommended for infections:

- Pancreatitis
- Anaphylactic reaction, IRR (including deaths)

The following adverse reactions have been identified during post-approval high concentrations of daratumumab; therefore, the incidence of antibody limitations in detecting anti-daratumumab antibodies in the presence of neutralizing antibodies against daratumumab. However, this assay has administered DARZALEX as combination therapy, developed transient monotherapy patients, and 2 of the 1,383 evaluable combination therapy in clinical trials of patients with multiple myeloma treated with DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials. Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

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 may be misleading.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,383 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZAEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Postmarketing Experience

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

Immune System disorders: Anaphylactic reaction, IRR (including deaths)

Gastrointestinal disorders: Pancreatitis

Infections: Cytomegalovirus, Listerialis

**Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX**

<table>
<thead>
<tr>
<th></th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>92</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>13</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

**DRUG INTERACTIONS**

**Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)**

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding [see References] or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

**Interference with Serum Protein Electrophoresis and Immunofixation Tests**

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy Risk Summary**

**Clinical Considerations**

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

**Data**

Animal Data

Male rats were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetal-maternal immune tolerance (mice), and early embryonic development (frogs).

**Lactation Risk Summary**

There is no data on the presence of daratumumab 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 circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for use during pregnancy.

**Females and Males of Reproductive Potential**

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models [see Data]. There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the 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.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

**Interference with Serum Protein Electrophoresis and Immunofixation Tests**

Concomitant use of DARZALEX with lenalidomide, pomalidomide, or thalidomide may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

**Data**

Animal Data

Male rats were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetal-maternal immune tolerance (mice), and early embryonic development (frogs).

**Lactation Risk Summary**

There is no data on the presence of daratumumab 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 circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for use during pregnancy.

**Females and Males of Reproductive Potential**

DARZALEX can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

**Pregnancy Testing**

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.
Contraception
Advised females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

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

Geriatric Use
Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients [see Adverse Reactions]. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

PATIENT COUNSELING INFORMATION
Advised the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions
Advised patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing [see Warnings and Precautions].

Neutropenia
Advised patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia
Advised patients to contact their healthcare provider if they notice signs of bruising or bleeding [see Warnings and Precautions].

Interference with Laboratory Tests
Advised patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation
Advised patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again [see Adverse Reactions].

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

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864
© 2015-2021 Janssen Pharmaceutical Companies

cp-271933v2
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 of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

The combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide 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 (15)]. The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO [see Dosage and Administration (2.1) in Full Prescribing Information].

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 [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 Warnings and Precautions].
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADIES [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 pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increase.

The most common adverse reactions (>20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADIES.
**Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
</tr>
</tbody>
</table>

a Fatigue includes asthenia, and fatigue.
b Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
c Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
d Bronchitis includes bronchitis, and bronchitis viral.
e Dyspnea includes dyspnea, and dyspnea exertional.
f Cough includes cough, and productive cough.
g Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:
- **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**: influenza, sepsis, 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 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

**Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>83</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
</tr>
</tbody>
</table>

a Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), fetomaternal immune tolerance (mice), and early embryonic development (frogs).

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 embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

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

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase 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 circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal 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 from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

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

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 231 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia. Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were ≥75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diaphoresis, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 133 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension. No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES


PATIENT COUNSELING INFORMATION

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

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, and blurred vision [see Warnings and Precautions].

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

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

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].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

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

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

Product of Switzerland

Manufactured by:
Janssen Biotech, Inc., Horsham, PA 19044
U.S. License Number 1884
© 2021 Janssen Pharmaceutical Companies

cp-26781v2
So quite a bit of follow-up. The median overall survival [OS] was 12.4 months in the pola-BR group vs 4.7 months only in the BR group. In the pola-BR extension cohort, the median OS was 12.5 months. That is about a year’s worth of survival for these patients. Again, these patients are beat up and have gone through a lot. Remember that in the SCHOLAR trial that came before all these newer agents, the median survival was about 6 months, so at least all these newer agents have incrementally improved upon the survival that we had historically.

As far as [adverse] events [AEs] are concerned, I think the general flavor that we get from pola-BR is cytopenias. So about half the patients [46.2%] experienced grade 3/4 neutropenia, 41% had thrombocytopenia, and 10.3% had febrile neutropenia, even in the BR arm. I think this is more a function of bendamustine. Then a few gastrointestinal [GI] issues that were mostly lower grade. There were also some cases of peripheral neuropathy, which can be caused by polatuzumab, but it was mostly all grades with no grade 3/4 events. The pola-BR group had a 33% discontinuation rate compared [with] only 10% in the BR group. In the pola-BR group, 13% of dose reductions were of BR and only 5% reductions of pola. So things that you might see if you used this regimen would likely be cytopenias and perhaps lower-grade neuropathy.

### Have you used tafasitamab plus lenalidomide?

Tafasitamab is an Fc-enhanced anti-CD19 monoclonal antibody. Obviously, we’ve had CD20 monoclonal antibodies for a long time. The first anti-CD19 treatment was blinatumomab [Blincyto] for B-cell ALL [acute lymphoblastic leukemia]. We now have more antibodies against CD19, which is a good target to use because it’s underutilized in the frontline and perhaps even the second-line setting.

[Although] there was an increase in antibody-dependence toxicity and phagocytosis, there was also direct cell death and some encouraging activity in [patients with] NHL [non-Hodgkin lymphoma], leading to the approval of tafasitamab for indolent lymphomas. This was followed by studies of the combination of tafasitamab with lenalidomide, which has efficacy in some of these patients; there was T- and NK [natural killer]-cell activation and expansion, as well as direct cell death.

This combination was further evaluated in the phase 2, single-arm, open-label, multicenter L-MIND trial [NCT02399085]. Eligible patients had to have had 1 to 3 prior lines of therapy, and transplant-eligible and primary refractory patients were excluded from this trial.

Tafasitamab was given at a 12 mg/kg weekly for cycles 1 through 3. There was another infusion of a loading dose of tafasitamab on day 4 of the first week, but then it was just weekly infusions for the 3 cycles. For cycles 4 to 12, tafasitamab was given every 2 weeks. Lenalidomide was administered at 25 mg per day for 3 weeks [days 1-21], followed by a week off for 1 year. At the end of the year, if patients have stable disease or better, lenalidomide falls off and patients continue with maintenance tafasitamab every 2 weeks until progression or toxicity-related discontinuation.

The median age was 72 years [range, 41-86]. About half the patients had a lower IPI risk score, and most [75%] had stage III to IV disease. The median prior therapy line was 2 [range, 1-4], with most [93%] having had 1 or 2 prior lines of therapy and not many [7%] having had 3 to 4. A minority of patients [19%] had primary refractory disease, about half were refractory to the last prior line of therapy, 11% received a prior transplant, and 10% had GCB.

At the 35-month follow-up, 40% had a CR, 17.5% a PR, and 16.3% each had SD [stable disease] and PD [progressive disease]. The ORR [overall response rate] was 57.5%, with quite a good median DOR of 43.9 months. The median time to response was 2.1 months.

The subgroup analysis showed similar responses. The Ann Arbor stage or age made no difference. Patients with low and low-intermediate IPI risks scores had slightly
better responses than patients with higher IPI risk scores, which makes sense. Patients with a non-GCB phenotype had a better response. This is probably due to lenalidomide. Non-GCB patients are dependent on the B-cell receptor pathway, and lenalidomide downregulates NF-κB [nuclear factor–κB] and other pathways and has activity in the ABC subtype.

The response was 71% vs 49% for the patients with a GCB phenotype, respectively. There was not much difference based on refractoriness to rituximab, last line, and primary refractory disease. Patients with only 1 prior line of therapy had a 70% response rate vs 50% for patients with at least 2. So there are a few trends emerging, which help us choose the right regimen for patients.

The median PFS at a median of 33 months of follow-up was 11.6 months, and the median OS at a median of 42.7 months of follow-up was 33.5 months. PFS was best for patients who achieved a CR. When that was not reached, the median PFS was 7.4 months for patients with a PR and 2.1 months for patients who were progressing very poorly. Same thing for OS, NR for the complete responders, and almost 2 years [22.5 months] for partial responders. For those that it works for, it works very well and for quite some time. Pretty useful regimen for some patients at least.

There were some hematologic AEs, with the most common being neutropenia, anemia, and thrombocytopenia. In particular, 27% of patients had grade 3 neutropenia and 21% had grade 4. Some patients have a febrile neutropenia risk, about 10% with grade 3 and 2% grade 4.

That is generally from lenalidomide, especially in the beginning. Those who have used it can probably appreciate the neutropenia that can be seen in the first few cycles. Growth factor and antimicrobial prophylaxis can be done for these patients. Another option is dose reductions; 25 mg/day can be a pretty hefty dose for some patients with DLBCL, perhaps older patients, heavily pretreated, if they have marrow infiltration.

The most common nonhematologic AEs were fatigue, GI issues, cough, pyrexia, peripheral edema, urinary tract infection, and decreased appetite. But there weren’t many grade 3 and 4 AEs. The only thing that generally we look for is cytopenias in the beginning. Even infusion reactions, not that many patients have it. In fact, you don’t even have to give the premeds if they haven’t had an infusion reaction by infusion No. 3.

The rate of serious AEs was 51%, and that of treatment-related discontinuation was 12%. The rate of TEAEs [treatment-emergent AEs] leading to death was 13%. Almost half of patients [45.7%] had at least 1 dose reduction of lenalidomide, perhaps from the neutropenia. About two-thirds of the patients [77.5%] were able to continue on the 20-mg per day lenalidomide dose.

Neutropenia is the main AE, with grade 3/4 events during the tafasitamab-and-lenalidomide combination phase, up to 12 cycles, with a median exposure of 6.5 months. In the next phase, patients go on to tafasitamab monotherapy [n = 37]. The median exposure for the extension group was 8.7 months. During this phase, there is neutropenia as well as other issues, but not as robust as in the beginning.

**How do you use loncastuximab tesirine for your patients?**

All responders have never used it, which makes sense [because] this is an even newer regimen than the other ones that we discussed. Lonca is another anti-CD19 drug conjugate. The CD19 antibody delivers SG3199, a cytotoxic DNA minor groove interstrand crosslinking a PBD [pyrrolobenzodiazepine] dimer payload as the inhibitor.

[Supporting data come from] the single-arm, phase 2 LOTIS-2 clinical trial [NCT03589469]. The eligibility criteria were similar to the previous studies [discussed]: adult patients with R/R DLBCL with at least 2 previous lines of therapy; a biopsy to show that the patient was still CD19 positive if a prior anti-CD19 therapy was used; ECOG performance status of 0 to 2; transplant-eligible patients were allowed; patients who received an autologous stem cell transplant 30 days prior or an allogeneic stem cell transplant 60 days prior were also permitted to enroll.

This is a single-agent drug. The first 2 cycles were given at a 0.15-mg/kg dose. Afterward and up to cycle 12—a 1-year treatment—the dose was 0.075 mg/kg. Follow-up was done for 3 years.

The median age was 66 [range, 56-71], and most of the patients had DLBCL. Hybrid B-cell lymphoma was allowed, so patients with double- and triple-hit disease were allowed in this trial, including double/triple expressors [14%], double/triple hit [10%], and 20% had transformed disease. Two-thirds of the patients [77%] had stage III or IV disease, 33% had a GCB phenotype, and 67% had either non-GCB or other phenotype. Patients had 2 [43%], 3 [24%], or more than 3 [32%] prior lines of therapy. In terms of treatment history, 68% had relapsed after the first line of therapy and 17% were refractory to all prior lines of therapy.

About a quarter of enrolled patients [25%] had received prior transplant therapies, of which 9% had CAR T-cell therapy prior to receiving Lonca on this trial. This was one of the first anti-CD19–directed therapies used after CAR T, so we can appreciate how those responses might have been. From a total of 145 patients, the ORR was 48% [95% CI, 39.9%-56.7%], 24 patients each for CRs...
and PRs. The median time to first response was 41 days [IQR, 38-44], so pretty quick. Of the 35 CRs, 57% had maintained the CR at data cutoff, so we’ll have newer data going on longer. Most responders had a response by 2 cycles, and the median [number of] cycles was about 4.5. 8

The most updated median DOR was 13.4 months. For the patients who were in CR, the median DOR had not been reached, while at the time of the initial data cutoff, it was 13.4 months. Patients with CRs do pretty well as far as the curves are concerned. 9

In the subgroup analysis, there are a few trends emerging. Patients with transformed or de novo disease responded almost equally. There were some differences between patients who had double- or triple-hit disease compared with those who did not, but patients did respond pretty well, even if they had transformed disease. Cell of origin and expression didn’t really matter. Even the hybrid B-cell lymphomas responded too, which is a particularly difficult population to study, as we’ve all experienced.

Most of the patients with R/R status after the first, last, or any lines did well. Another important feature was whether prior transplant and CAR-T therapy made a difference in response. Prior transplant and CAR-T therapy also didn’t seem to matter, so pretty good addition to our armamentarium for treatment of these particularly problematic patients that can be useful in a lot of these situations. 8

What is interesting in this study is that patients were tracked even if they continued on to later lines of therapy, including 15 patients who received CD19-directed CAR-T therapy with an ORR of 46.7% and 9 who received stem cell therapy as consolidation. 8, 9 You can certainly take patients to CAR T even after receiving loncastuximab, and stem cell transplant can obviously be used to stabilize the disease. These subsequent treatments not only can improve lead progressive treatments, but can also serve as a segue into further lines of therapy for some patients.

Challenging subgroups include high-grade [HG]BCL and post-CAR-T therapy. As far as HGBCLs are concerned, 11 patients had CR. Compare to that at the patients with DLBCL, 24.4% had a CR, and 26% had a PR. Again, pretty good responses for those patients. Time to first response was similar between the 2 groups [approximately 40 days]. However, HGBCL took longer to get to a CR, approximately double the time than that for patients with DLBCL.

For patients who went on Lonca after CAR T-cell therapy relapse [n = 13], the response to CAR T-cell therapy was about 54% CRs, 15% PRs, and 30% no response. These patients then went on to receive Lonca after CAR T-cell therapy, and [about 45%] achieved either a CR or PR. 9 The most common AEs were B-cell neutropenia [26.2%], thrombocytopenia [17.9%], GGT [γ-glutamyl transferase] increase [17.2%], and some anemia [10.3%]. Treatment discontinuation occurred in about 17.9% of patients, and most commonly was either because of surface edema, localized edema, or GGT increase. There was no increased toxicity in the older population, which is why dexamethasone [4 mg twice a day] is generally given as a premedication [a day before loncastuximab], and patients shouldn’t go out in the sun either.

Treatment delays and dose adjustments were allowed. Patients with weight gain of more than 1 kg from day 1 of cycle 1 or with edema/pleural effusions received standard doses of spironolactone. Peripheral edema was seen in about 16% of the patients, with not much difference [seen] between patients [older than] 65 years and those [younger than] 65 years. 9

REFERENCES
Lisberg Examines the Role of Adjuvant Therapy in NSCLC

**CASE SUMMARY**

An otherwise healthy White woman, aged 60 years, presented with a nonproductive cough. She was a former smoker who quit 8 years ago (13 pack-years). She had an ECOG performance score of 0, blood pressure 120/93 mm Hg, heart rate of 75 beats per minute, body mass index of 22, and lungs were clear to auscultation bilaterally. All laboratory results were within normal limits. A chest x-ray revealed a 5.5-cm right mass in the right upper lobe of the lung, and a CT chest/abdomen scan showed a lobulated 5.5 × 5.1-cm mass in the right upper lobe.

A biopsy of the right upper lobe revealed thyroid transcription factor-1–positive adenocarcinoma consistent with non–small cell lung cancer (NSCLC). PET results were negative for any spread to lymph nodes or distant metastasis. A brain MRI result was negative and pulmonary function tests were normal.

The patient underwent a right upper lobectomy without complications. Pathology showed she had a 5.5-cm tumor with negative margins, node negative, and a pathologic stage IIB (ptT3N0M0) lung adenocarcinoma. Her ECOG performance status was now 1.

**DISCUSSION QUESTIONS**

• What are the challenges and barriers to testing?
• Who on the multidisciplinary team orders molecular testing?

**POLLING QUESTION**

“Are you routinely ordering molecular testing for early-stage non–small cell lung cancer?”

- Yes: 70% (7)
- No: 30% (3)

Total votes: 10

**LISBERG:** What are the challenges and barriers to testing? Can someone please share with us—maybe someone involved with molecular testing in the frontline setting? What challenges or barriers have they had in terms of doing the testing, and then if we can also get a sense for who on the multidisciplinary team is ordering molecular testing?

**CHARU:** I don’t find many challenges to ordering the molecular testing. I usually send it for next-generation sequencing [NGS], and I am the one who’s ordering and telling the pathologist to send it. Once I see the patient, then I must call [the pathologist] and ask them to send the specimen.

**MILANI:** In general, the oncologist is performing the testing, and I don’t necessarily see it as a barrier or challenge. It’s more of a timing matter, in terms of receipt of the result. I think that would be the biggest challenge.
For our multidisciplinary team, because we engage in subspecialization at Kaiser Permanente West Los Angeles [Medical Center], it’s the oncologist who is performing the testing.

**LISBERG**: Are you having significant delays that affect the way you [treat] patients? What’s your typical turnaround time for these types of tests?

**MILANI**: With immunohistochemistry it’s a little easier, but I would say 1 to 2 weeks. It would be nice to have all this information when the patient comes in for the initial consultation. Patients are quite savvy now; I even have patients who [come in with] the patient version of the National Comprehensive Cancer Network [NCCN] guidelines on their first visit. They’re data-driven and so they expect to have that on initial receipt of postsurgery [results] and even biopsy. It’s a confidence-building measure for patients to see the oncologist have that applicability of information on their first visit. I think it’s more of those barriers or challenges as opposed to getting the testing ordered.

**LISBERG**: What kind of testing panel are you sending?

**MILANI**: We use NeoGenomics Laboratories and either Strata Oncology or Tempus, and liquid biopsy when required.

**LISBERG**: Dr Sweet, what are you doing at your institution?

**SWEET**: Part of this discussion makes me think how different lung cancer is. Our pathologists have always been resistant, except in breast cancer, to do the molecular testing as part of the routine pathology work-up. Historically, [pathologists have] been resistant for [various] reasons, especially because they didn’t know whether the patient was metastatic.

But, for [most] patients now, if knowing all these markers are critical to even early-stage management, I think the pathologists should do this as an automatic routine. It would save time.

**LISBERG**: How much time do you think is added on because the pathologist isn’t doing it reflexively in your system?

**SWEET**: It varies. It could be a good week to 2 weeks. It disrupts the patient’s confidence when you meet the patient and say, “Well, there’s more information that I need. We have to wait.” Yet, there’s this other dynamic in our system to get that patient seen as soon as possible, even in advance of having all the detailed information on the back end.

Historically, I think the rationale is that we were generally looking at markers for advanced disease. They didn’t know who was advanced and who wasn’t. They could spend some time looking at the clinical picture but they prefer not to. They just want to look at the specimen.

You could argue then [that] if a lung specimen comes in it should be reflexively assessed for all these known markers. We’ve been doing it in breast cancer for 40 years. They rapidly adopted HER2 as a standard and as we’re learning, we’re going to see other standards that involve biomarker-driven or genetically driven treatments, even in early stage.

**LISBERG**: I agree with everything you’re saying. Clearly, EGFR testing is critical because it changes our management. You could argue whether some of the other molecular testing is critical in the early stage, but I agree with you. Those trials are ongoing, and we anticipate that those could be practice changing.

**VORA**: The only thing I’d add is we’ve made a concerted effort to meet with our pathologist and share the early-stage data with them; combine that with the conversations we had in the past about advanced diseases and how important it was to have the molecular testing. The rule now is to have all lung cancer specimens sent out for NGS automatically. We’re using Tempus as the platform, and we’ve talked to Tempus and had them come to meet with our pathologist, and it’s a good system setup.

I can recall having a patient who [received a diagnosis] in an outside hospital and they didn’t do reflexive testing on lung cancer specimens. There was a significant delay in treatment, even with the patient having advanced-stage disease. I think the thinking from that hospital was, they got burned once upon a time where they ran these tests, and it didn’t get used or the patient ended up not getting treatment. They are very cost-conscious and are waiting for the order before they send off these tests.

Those are the only challenges. I feel like in the early-stage [setting] of lung cancer, we have time to wait, based on the EGFR testing, because some of these patients are getting adjuvant chemotherapy. If I get the results after 3 to 4 months, I feel comfortable, and I don’t think there’s much delay in treatment in those cases.

**DISCUSSION QUESTIONS**

- What is the role of adjuvant chemotherapy in your practice? What are the treatment goals?
- Which regimen(s) do you typically employ?
- Which parameters are important when deciding whether to use adjuvant systemic therapy post resection? Do you consider tumor size, number of metastatic nodes, or histological poor-risk features?
**LISBERG**: What is the role of adjuvant chemotherapy in your practice? What are the treatment goals?

**STEPHEN**: I don’t have a huge population of patients with lung cancer, but when I do it’s a moving target. Who qualifies for adjuvant therapy at this point? I just go to the [NCCN] guidelines and run through the most recent data, considering the typical goals of adjuvant therapy. If it is after their chemoradiation, if they’re willing to accept the toxicities of additional chemotherapy, then we go down that path. I offer it to whoever’s eligible and willing.

**LISBERG**: Given the patient population you have, what were your answers for the node-positive and for the node-negative but large tumor populations? What percentage of those patients would you say you give adjuvant chemotherapy?

**STEPHEN**: I choose the highest percentage for patients with node-positive disease and I put the next highest percentage for those with large tumors.

**LISBERG**: What is the thought process behind that?

**STEPHEN**: The node-positive disease is what I’ve seen more as an indication for typical patients who require adjuvant therapy, so it’s what I’m used to. I’d have to look back at patients with larger tumors [as to] who exactly qualifies.

**LISBERG**: That makes sense. Which regimens do you typically use for adjuvant chemotherapy?

**STEPHEN**: It depends on adenocarcinoma vs squamous cell carcinoma [histology]. I haven’t been using any targeted treatment yet, so it’s been more immunotherapy and chemotherapy.

**LISBERG**: Dr Abdulla, can you tell us the role of adjuvant chemotherapy in your practice, treatment goals, and what types of regimens you use?

**ABDULLA**: I do follow NCCN guidelines, so I try to do adjuvant chemotherapy to those who qualify for it, those with stage IB [disease] and above. The treatment goal is to get them through their recommended treatments and improve their overall survival.

I try to incorporate mostly cisplatin, compared with carboplatin, when I’m using treatment. Then maybe I’ll consider pemetrexed [Alimta]. Or, with a patient with squamous cell carcinoma, I would consider a taxane-based combination treatment, but I have recently been trying to do mutation testing for patients in the adjuvant setting and ordering NGS myself.

**LISBERG**: If you’re deciding for or against adjuvant chemotherapy, which factors are most important when making those decisions?

**ABDULLA**: The No. 1 factor is the lymph node status. We do have confusion on the tumor size; if it is less than 4 cm, then I’m trying to [consider] these high-risk features, like pleural invasion, lymphovascular invasion. Whenever we have a patient who doesn’t meet the criteria, the best thing is to discuss their cases with the tumor board and our pathologist. Sometimes we learn that there are now more features, which will guide our treatment. I have learned a lot discussing these cases, especially the borderline cases, in a tumor board meeting.

**LISBERG**: Do you discuss most of your patients with early-stage NSCLC in the tumor board, or just the ones where you’re on the fence?

**ABDULLA**: In our practice, we try to do all of them.

**LISBERG**: I always find that the discussion about adjuvant therapy can go in different directions, depending on the patients. How do you typically approach that discussion? Are there certain factors that push you to make your recommendation stronger, or certain areas where you may be more comfortable with not doing anything? How do those discussions go, in your experience?

**ABDULLA**: Whenever I have a patient, or when I’m discussing adjuvant treatment, I show them graphs available online to show the risk of recurrence, which is high. Even in those patients whose disease is treated with resection, the risk rate comes up to be 50% to 60%.

Most of the patients are recurring. That’s a major driver. I try to find whatever data we have about adjuvant treatment, and then show them, “You still would have a chance of recurrence, but at least you would decrease the chances.” I am more visual; I try to show them graphs. For some of the patients, I have had issues in going too much in detail; I guess they rely on the physicians who manage them.

**LISBERG**: Dr Sam Yeh, what are your thoughts about this? What’s the role for adjuvant chemotherapy in your practice, treatment goals, the regimens, and which factors do you weigh most heavily?

**S. YEH**: All are important: tumor size, node status is very important—Hilar node positive vs node negative. I think about other high-risk features if they’re node negative. They’re all important: age, performance status, and potential toxicity. If you add multiple factors together then they become more important.
I think the case that’s controversial is tumor size of 4 cm and node negative. Is there benefit for chemotherapy there, and if there is [then] do you use cisplatin or carboplatin? If they have EGFR mutations, do you use EGFR tyrosine kinase inhibitors plus immunotherapy? For patients with N1 node-positive status, I’m not very clear about [chemotherapy benefit].

LISBERG: All things being equal, if it’s a patient for whom you feel strongly you want to move forward with adjuvant chemotherapy, what backbone do you usually use?

S. YEH: I use platinum-based chemotherapy because that’s based on all the studies; cisplatin is the way to go. Pemetrexed is what I use for adenocarcinoma. Then, if it’s squamous cell carcinoma, I probably choose docetaxel.

LISBERG: In stage IIB, which is N0 or N1 disease with negative margins, the NCCN guidelines show chemotherapy and osimertinib [Tagrisso] as a category 1 recommendation.¹ The guidelines for adjuvant chemotherapy, modified for the eighth staging edition, refer to or reflect on a lot of what we’ve already been talking about. Importantly, in stage IA disease, observation is recommended.

In stage IB, [it is] observation or chemotherapy for high-risk patients. So, it’s a bit of a hard decision to make, but we can personalize that to the patients. In stage IIA, [it is] observation or chemotherapy for high-risk patients. At stage IIB and higher, chemotherapy has level 1 evidence. It’s those earlier-stage patients where the decision is more of a discussion.

In terms of high-risk features [tumor size greater than 4 cm, vascular invasion, poorly differentiated tumors, visceral pleural invasion, wedge resection, and unknown lymph node status], they are prognostic but not predictive of benefit from adjuvant chemotherapy. I wouldn’t say it’s a data-free zone, but we don’t have great data to guide this decision.

DISCUSSION QUESTIONS

- Which parameters are important when deciding on whether to add adjuvant radiation therapy?
  - Tumor size less than 4 cm
  - Resection status
  - N2 disease
- Which patients should be referred to radiation oncology for evaluation?

H. YEH: I think all of these [factors] are important. I think surgeons would use tumor size, the extent of resection, and N2 status in their decisions on whether to resect. Often, we as oncologists get a consult like this because the surgeon thinks that the tumor site is too big, or may be invading other adjacent organs, or the lymph node metastasis has already spread to the opposite side, or it’s in the N2 category, they cannot resect. But, if it’s small from a surgical standpoint we do chemoradiation, that would be our recommendation.

LISBERG: Do you talk about this in a multidisciplinary conference and then refer to radiation oncology afterward? What’s the patient flow in these settings?

H. YEH: Typically, the radiation oncology staff is very experienced with these kinds of cases, and if there’s a tumor board, we discuss; but if not, I think referral to radiation oncology would be sufficient.

LISBERG: Great. Dr Lorber, can you share your thoughts on which patients you use radiation for in the adjuvant setting, and the workflow of how those patients get there?

LORBER: It’s rare and restricted to those with margin positivity. The workflow is either to discuss at the tumor board after the surgery or just refer directly to the radiation oncologist.

LISBERG: I agree. In many cases—obviously we’re not using radiotherapy as frequently as chemotherapy, or targeted therapies—there clearly is a role based on those NCCN guidelines.¹

CASE UPDATE

Following resection, the patient receives 4 cycles of adjuvant chemotherapy with cisplatin and pemetrexed. Her ECOG performance status is 1. Molecular testing discovers an EGFR exon 19 deletion.

POLLING QUESTION

“Would you consider an adjuvant EGFR tyrosine kinase inhibitor in this patient?”

<table>
<thead>
<tr>
<th></th>
<th>100% (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Unsure</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

Total Votes: 11

DISCUSSION QUESTIONS

- What are your reactions to the data from the ADAURA trial (NCT02511106) of adjuvant osimertinib? Do you consider them practice changing?
- What are the strengths and weaknesses of the study, and what are the pros and cons of this strategy?
**LISBERG:** What are your reactions to the ADAURA data?

**OU:** ADAURA is paradigm changing. Results were [published in] the *New England Journal of Medicine.*\(^3\) It’s [led to approval of adjuvant osimertinib] by the FDA for stage IB to IIA NSCLC [for patients with *EGFR* exon 19 deletions or exon 21 L858R].\(^4\)

I don’t have any problems with that. I’m a true believer because it dovetails into a bigger [question] of lung cancer screening in patients who are never-smokers [From The Data].\(^5\) One of the things [individuals] say is that you don’t screen because we can’t find [which] patients with lung cancer are smokers, and that’s not true. Hopefully, in 2022, we will present some data in a meta-analysis, but if we detect disease in the early stage, then osimertinib improves disease-free survival [DFS]; there is no question about it. That’s it, there are no weaknesses.

Patients are not stratified for adjuvant chemotherapy or not, so the free stratification factors did not include adjuvant chemotherapy. A paper in the *Journal of Thoracic Oncology* shows, essentially, [that patients in ADAURA who received] adjuvant chemotherapy [before receiving osimertinib] had no benefit to DFS [vs those who did not receive adjuvant chemotherapy before osimertinib].\(^6\)

That’s just from looking at the absolute numbers, stage by stage. You can plot the bar graph and they are the same. It is practice changing, and this will point the way to other adjuvant therapies to check for not just *EGFR* but *ALK, ROS1, NTRK, MET* exon 14, [and other targets]. It is huge. You can see the DFS, [though] whether it’s 3 years, 5 years, [or] indefinite is the key.

[In terms of] financial toxicity, in the United States, it’s either covered by insurance, or you have patient assistance programs. Financial toxicity is not a real issue [for this].

**LISBERG:** The data from the *Journal of Thoracic Oncology* are very interesting. I think it’s an open question, because certainly, from a quality-of-life perspective and toxicities, all of us would like to avoid adjuvant chemotherapy if possible in our *EGFR*-positive patients. I don’t know whether the data are there, and I think that it’s a subgroup analysis, but it’s very interesting.

---

**REFERENCES**

The patient initially received a diagnosis of a clinical stage IA (T1N0) left breast hormone receptor-positive (HR+), HER2-negative (HER2–) invasive ductal carcinoma. Given the small size of the tumor and without evidence of lymph node (LN) involvement on imaging, we would recommend upfront surgery with a plan for adjuvant systemic therapy tailored to the final surgical pathology. If considering preoperative systemic therapy, then we would strongly consider use of a gene expression assay to guide the choice of systemic therapy (ie, neoadjuvant endocrine therapy vs chemotherapy). However, in this clinical scenario, upfront surgery to better guide adjuvant treatment strategy is indicated.

After lumpectomy and sentinel LN biopsy were completed, the pathologic stage was IIB (T2N1). If whole-breast irradiation is planned, axillary LN dissection may be omitted per ACOSOG Z0011 (NCT00003855) trial criteria. The 21-gene assay recurrence score is used to determine adjuvant systemic therapy. Given the patient’s RS of 31, we would recommend adjuvant chemotherapy, followed by adjuvant endocrine therapy. Unfortunately, results from the TAILORx (NCT00310180) and RxPONDER (NCT01272037) trials evaluating the omission of adjuvant chemotherapy in select patients cannot be applied to this case.1,3,4

TAILORx only included patients with node-negative disease, whereas, RxPONDER trial randomly assigned patients with 1 to 3 lymph nodes involved with an RS of 25 or less to adjuvant endocrine therapy vs adjuvant chemotherapy plus endocrine therapy. Although RxPONDER showed that postmenopausal women with up to 3 axillary lymph nodes involved and an RS of 25 or less did not benefit from adjuvant chemotherapy, this patient does not meet this criteria with an RS of 31.

Furthermore, previous analysis of the results of the SWOG-8814 trial (NCT00929591) showed that postmenopausal women with LN involvement and an RS of 31 or more who were given chemotherapy plus tamoxifen had a survival benefit over those receiving tamoxifen alone.5 Therefore, we would recommend adjuvant chemotherapy in addition to adjuvant endocrine therapy in this case. Per analysis of results of the ABC trials, it would be reasonable to offer docetaxel plus cyclophosphamide rather than doxorubicin, cyclophosphamide, and taxane, given the tumor size and limited number of LNs involved.6 After chemotherapy, whole-breast irradiation would be recommended because the patient underwent lumpectomy rather than a mastectomy. The decision to give regional nodal radiation should be individualized in the setting of 1 to 3 positive LNs.

After completion of radiation, we would recommend adjuvant endocrine therapy (ET) with an aromatase inhibitor (AI), given lower rates of breast cancer recurrence and 10-year breast cancer mortality with AIs compared with tamoxifen in postmenopausal women.7 The AI should be given for a minimum of 5 years. After considering drug tolerability and patient preferences, we would offer an additional 5 years of adjuvant AI, in
keeping with current American Society of Clinical Oncology (ASCO) clinical practice guidelines for patients with LN involvement. In addition to adjuvant endocrine therapy, olaparib (Lynparza) and abemaciclib (Verzenio) recently have been approved for use in the adjuvant setting for select patients with high-risk, early-stage HR+ breast cancer. The phase 3 OlympiA trial (NCT02032823) was for patients with HER2−, high-risk, early-stage breast cancer and germline BRCA1/2 mutations. After receiving chemotherapy, patients were randomly assigned to adjuvant olaparib vs placebo for 12 months. Patients who received olaparib had improved 3-year disease-free survival (DFS) compared with placebo (86% vs 77%; \(P < .001\)) with a recently reported overall survival (OS) benefit at 3.5 years of median follow-up. Importantly, the OlympiA trial defined patients with high-risk HR+ disease as those with at least 4 positive LNs being treated with adjuvant chemotherapy or those without a pathologic complete response to neoadjuvant chemotherapy with a CPS + EG score of 3 or higher. Based on these criteria from OlympiA and the FDA indication for adjuvant olaparib in HR+, HER2− breast cancer, the patient would not be eligible for adjuvant olaparib even if she was found to have a germline BRCA1/2 mutation. Conversely, we would recommend adjuvant abemaciclib for 2 years concurrently with adjuvant AI for this patient based on the results of the monarchE trial (NCT03155997). In this open-label phase 3 study, more than 5000 patients with early-stage HR+, HER2− breast cancer were randomly assigned to standard-of-care adjuvant ET plus abemaciclib at 150 mg twice daily for 2 years vs ET alone. For trial eligibility, patients were required to have high-risk disease defined as 4 LNs involved or 1 to 3 LNs plus at least 1 of the following: tumor 5 cm or larger, histologic grade 3, or Ki-67 20% or more. At follow-up analysis, the absolute improvement in 3-year invasive DFS of abemaciclib over ET alone in the intent-to-treat (ITT) population was 5.4 percentage points. The benefit was even greater in patients with a high Ki-67 index with a statistically significant improvement in 3-year invasive DFS of 86.1% vs 79% with the addition of abemaciclib to ET. Although the survival data showed no benefit of abemaciclib in the ITT population (hazard ratio, 1.091; 95% CI, 0.818–1.455), OS data are immature and longer follow-up is required. The FDA approved adjuvant abemaciclib in combination with ET for those with high-risk disease per monarchE criteria and a Ki-67 of 20% or more.

The patient in this case fits these criteria and therefore should be offered abemaciclib for 2 years along with adjuvant endocrine therapy. Of note, we may also consider adjuvant abemaciclib in patients with high-risk disease defined by monarchE criteria as 4 or more positive axillary LNs or 1 to 3 positive axillary LNs and 1 or more of the following features: histologic grade 3 disease, tumor size 5 cm or larger, or Ki-67 index 20% or more per the 2021 American Society of Clinical Oncologists Rapid Recommendation Update. When considering adjuvant abemaciclib in patients with early-stage HR+, HER2− breast cancer, clinicians must consider clinicopathologic features and the risk of breast cancer recurrence, expected increase in toxicities with the addition of abemaciclib to adjuvant endocrine therapy, and patient preferences. The pros and cons of adjuvant abemaciclib in combination with ET must be discussed with the patient. Although the patient’s overall prognosis is favorable, the addition of abemaciclib for 2 years in addition to adjuvant AI for at least 5 years may further reduce the risk of breast cancer recurrence. Common adverse events (AEs) of abemaciclib include diarrhea, neutropenia, and fatigue, as well as the rare but notable AEs of interstitial lung disease (3.2%) and venous thromboembolism (2.5%). Adjuvant abemaciclib should be discontinued if the AEs remain intolerable despite supportive care interventions or dose adjustments with continuation of adjuvant endocrine therapy.

For full list of references, visit TargetedOnc.com/Link/1888
Targeted Oncology™ is proud to celebrate 10 years of providing oncology health care professionals in community settings with the most up-to-date information through innovative learning formats and valued peer-to-peer engagements.

The treatment landscape has evolved tremendously over the past 10 years with advances in genetic testing and targeted therapies to complement standards of cancer care. The horizon continues to brighten as research, trials, and approved therapies have advanced quickly and bring hope to patients and their loved ones.

We are fully committed, along with the broader oncology community, to another decade of driving knowledge, empowering change, and optimizing outcomes.

A Decade of Transformational Therapies
Join us throughout 2022 as we look back on the impact made in 10 clinical focus areas.

Get Social

@TargetedOnc  @TargetedOnc  @TargetedOnc
Rettig Reviews Systemic Therapy Options for mCSPC

CASE

• A 73-year-old man presented with urinary retention, fatigue, and decreased appetite.
• He has a family history of prostate cancer.
• He is active and is very involved in his grandchildren’s activities.
• Transrectal ultrasound and biopsy reveal adenocarcinoma of the prostate gland; Gleason score 8 (4 + 4) with disease in 10 of 12 cores.
• Prostate-specific antigen (PSA), 150 ng/mL; hemoglobin (Hb), 9.7 g/dL; absolute neutrophil count (ANC), 1.9
• Liver function tests are abnormal.
• Patient received diagnosis of localized high-grade prostate cancer.
• He undergoes robotic radical prostatectomy with subsequent PSA levels decrease (0.2 ng/mL).

• CT and bone scans showed no residual disease.

13 months later

• Patient complains of right hip pain and abdominal pain.
• Imaging with CT and bone scan show multiple metastatic bone lesions in the pelvis and diffuse liver lesions.
• PSA, 90 ng/mL; Hb, 9.4 g/dL; ANC, 1.5
• Patient receives diagnosis of metastatic prostate cancer.
• Germline genetic testing is negative.
• He wishes to receive oral treatment and avoid chemotherapy; minimizing adverse events (AEs) is very important to him.

Matthew B. Rettig, MD
Medical Director, Prostate Cancer Program
Institute of Urologic Oncology
University of California, Los Angeles
Los Angeles, CA

POLLING QUESTION

“What systemic treatment option are you most likely to recommend for this patient?”

- ADT + abiraterone 40% (4)
- ADT + enzalutamide 30% (3)
- ADT + docetaxel 10% (1)
- ADT alone 10% (1)
- Other/c clinical trial 10% (1)
- ADT + apalutamide 0% (0)

Total votes: 10

Targeted Oncology™: What do the National Comprehensive Cancer Network (NCCN) guidelines recommend for patients with metastatic castration-sensitive prostate cancer (mCSPC)?

RETTIG: The NCCN guidelines for disease [with at least 1 metastasis] for mCSPC are based on level 1 evidence that androgen deprivation therapy (ADT) should be used with 1 of these 4 agents. The apalutamide [Erleada] and enzalutamide [Xtandi] can be used for any patient, irrespective of disease volume. Docetaxel, at least in the CHAARTED study [NCT00309985], was indicated for high-volume disease, as it was in our patient here, and it was a selection [in the poll]. Abiraterone [Zytiga] was approved based on the LATITUDE study [NCT01715285], which only enrolled high-risk patients. So they were high risk, [which is] very similar to high volume, except the threshold for bone disease is 3 or more bone metastases, with 1 outside the axial skeleton. The patient had to have either visceral disease or a Gleason score of at least 8. Most of the patients who have high volume have high risk and vice versa.

I want to emphasize that patients who are presenting with metastatic disease with their primary tumor, de novo disease—if they have oligometastatic or low-volume disease—should receive radiation to the primary tumor for an overall survival [OS] benefit. That was shown in the STAMPEDE [NCT00268476] and HORRAD trials, and in STAMPEDE there was an 8% absolute improvement in 3-year survival with radiation to the primary tumor. The rationale for that is that the primary tumor represents a continued source of metastases, and we know from autopsy series [that] when we sequence multiple metastases from a patient who has succumbed to prostate cancer and we create a genetic tree, what we can see is that metastases are derived from the prostate but can metastasize back to the prostate and then back out again.
So there is a rationale to remove the prostate, and there’s now empiric evidence to establish that it improves OS.\(^5\)

Low-volume disease is defined as not being high volume. High volume would be 4 or more bone metastases. If it were 3 or fewer, then we’d call that low volume.\(^1\)

How did the 4 approved therapies perform in clinical trials?

The hazard ratios for [abiraterone, enzalutamide, and apalutamide] are very similar.\(^4,5,7-9\) In the CHAARTED study, the hazard ratio was also in the 0.6 range for docetaxel, and that was for high-volume disease.\(^2\) The enzalutamide and apalutamide both show, if anything, slightly more benefit for the patients with high-volume disease.\(^7,10\)

So if a patient has high-volume disease, there is no requirement to use [docetaxel] chemotherapy. You can use, with similar efficacy, 1 of the hormonal agents. AEs leading to discontinuation were slightly higher with chemotherapy.\(^11\) These are all fairly well-tolerated agents.

What practical considerations are there for physicians prescribing the 4 approved agents for mCSPC?

Abiraterone and methylprednisolone are indicated for metastatic castration-resistant prostate cancer [mCRPC] and mCSPC.\(^12\) Apalutamide is indicated for mCSPC and nonmetastatic CRPC.\(^13\) Docetaxel is for mCRPC,\(^2\) and enzalutamide is for mCSPC and mCRPC, as well as nonmetastatic CRPC.\(^14\)

I would emphasize with abiraterone, you do have mineralocorticoid excess.\(^12\) Adrenal insufficiency would be attributable to the prednisone and not abiraterone; the drug does not cause adrenal insufficiency. It inhibits CYP17 even in humans that have complete absence of CYP17 due to a congenital adrenal hyperplasia; they do not develop adrenal insufficiency, they only develop mineralocorticoid excess. With enzalutamide and apalutamide, [because] these are older patients, I think you have to be careful with predisposing factors for seizures because they both can cause seizures.\(^13,14\) Patients who had predisposing factors for seizures such as stroke, transient ischemic attack, and prior seizure were excluded from the studies.\(^7,8\) I always ask my patients about that and let them know about a 0.5% risk of seizure.\(^13,14\) Risks of falls and fractures are also relevant in apalutamide and enzalutamide, because they’re more common in this population in general.

Please describe the design and goals of the TITAN trial (NCT02489318).

This was the phase 3 randomized controlled trial that led to the regulatory approval of apalutamide for this mCSPC patient population.\(^15\) The population included patients who had de novo or recurrent mCSPC. The patients had to have good performance status and they were required to be on ADT continuously.

They were allowed to have previously received docetaxel, and about 10% to 11% of the patients had received it.\(^7\) They had to be on ADT for less than 6 months if it was started from metastatic disease, or less than 3 years for local disease, and the treatment had to be completed 1 year prior in that case.

The patients were stratified per Gleason score, geographic region, and prior chemotherapy. It was a 1:1 randomization between December 2015 and July 2017 to apalutamide at the standard dose of 240 mg vs placebo, and there were coprimary end points of overall survival [OS] and radiographic progression-free survival [rPFS]. There were several secondary end points and some exploratory end points, including an interesting exploratory end point called PFS2, second progression-free survival.

<table>
<thead>
<tr>
<th></th>
<th>APALUTAMIDE ARM</th>
<th>PLACEBO ARM (INCLUDES CROSSOVER TO APALUTAMIDE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>170 (32.4)</td>
<td>235 (44.6)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>NR (NR-NR)</td>
<td>52.2 (41.9-NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.53-0.79)</td>
<td></td>
</tr>
</tbody>
</table>

\(P<.0001\)

\(NR\), not reached.

---

**Table. Final Overall Survival from the Phase 3 TITAN Trial**\(^{16}\)
I would be [suspicious] of saying that apalutamide added to docetaxel would [be of] benefit. It’s probably because of a drug interaction where apalutamide induces or activates CYP3A4, which metabolizes docetaxel, probably rendering docetaxel levels lower.”

—MATTHEW B. RETTIG, MD

What can you say about the patient population of this trial?
The [patients’ baseline characteristics] were well balanced. As we see in almost all of these studies, about 60% to two-thirds of the patients who enrolled in these trials have high-volume disease. Most of the patients had M1 disease at diagnosis. So that means they had de novo mCSPC, whereas the M0 patients had recurrent mCSPC. Most of them had appropriate performance status and a Gleason score of 7 or higher. If they had a Gleason score less than 7, that was an error. There is no such thing as a Gleason score 6 tumor that metastasizes; that’s probably either a miscategorization or the patient only had a prostate needle biopsy and did not have a radical prostatectomy, which will upgrade those Gleason score 6s in about 30% of the cases. Only about 10% to 11% of the patients had prior chemotherapy, and the baseline pain is fairly mild in this population—which also has a good performance status.

What was the OS observed in this trial?
We have OS data from the final analysis after 44 months [Table16]. This is from the Journal of Clinical Oncology, while I believe the original New England Journal of Medicine article presented data at 29 months.7 The data held up. The hazard ratio was almost identical as it was in the original article, and that’s a hazard ratio of 0.65 [95% CI, 0.53-0.79; P = .0001].16 The placebo arm reached about 4.5 years before crossing below the 50% OS rate.

The investigators did an analysis where they accounted for crossover from placebo to apalutamide, and if you exclude those patients who crossed over, the magnitude of the benefit is even higher.7 It’s an artificial way of looking at it, but that is the case. In addition to OS, it also markedly improved rPFS, time to PSA progression, time to castration resistance, and time to initiation of chemotherapy.7,17

In health-related quality-of-life [QOL] questionnaires that were administered during the study, the study staff were not allowed to help the patients. So they’re completed only by the patient, and it’s the patient reporting their true sense of their QOL. There was no difference in QOL [between the arms].16

What stood out about the subgroups in the TITAN trial?
There were about 110 patients with prior docetaxel use, and there’s clearly no benefit there in the docetaxel. There are too few patients, but given the data with ENZAMET [NCT02446405] with enzalutamide, where half the patients had prior docetaxel and there was no benefit.8 I would be [suspicious] of saying that apalutamide added to docetaxel would [be of] benefit. It’s probably because of a drug interaction where apalutamide induces or activates CYP3A4, which metabolizes docetaxel, probably rendering docetaxel levels lower. Overall, apalutamide is pretty easy to use and it benefited patients with low- and high-volume disease.16

How did apalutamide perform in terms of the trial’s secondary end points?
Time to chemotherapy was improved, but median time to pain progression was not; it did not reach statistical significance.7,17 The secondary end points were tested in a hierarchical fashion, so that once you get to pain progression, if it doesn’t reach a statistical significance, investigators don’t perform a statistical P value for the subsequent secondary end points of chronic opioid use and time to skeletal-related event.

What were the patient-reported outcomes in this trial?
The curves [for the apalutamide and placebo arms] for patient-reported outcomes overlap throughout the course.16 If anything, the apalutamide may be a little bit higher at the very end, but there’s certainly no decrement in the QOL based upon patient-reported outcomes. And I think that’s important to emphasize when telling patients. I certainly tell them that if you take apalutamide, you’re not going to feel any difference in your QOL vs if you didn’t take it.
WHY WAIT?

LEARN WHERE YOU CAN START OPDIVO IN THE TREATMENT CONTINUUM

Scan here to contact a BMS representative today.