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Roundtable Discussion: Education and Treatment of Patients With Myelofibrosis

CASE SUMMARY

A woman aged 68 years presented to her physician with symptoms of fatigue and abdominal pain lasting 4 months; she also reported increased bruising. Her spleen was palpable 8 cm below the left costal margin. Genetic testing showed a JAK2 V617F mutation and a bone marrow biopsy showed megakaryocyte proliferation and atypia with evidence of reticulin fibrosis. A blood smear revealed leukoerythroblastosis.

Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>3.40 × 10^5/µL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9.1 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>36%</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>94 µm^3</td>
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<tr>
<td>White blood cells</td>
<td>32,000/µL</td>
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<tr>
<td>Platelets</td>
<td>98 × 10^3/µL</td>
</tr>
<tr>
<td>Peripheral blood blasts</td>
<td>2%</td>
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</tbody>
</table>

POLLING QUESTION

“What risk-assessment tool do you use most often?”

<table>
<thead>
<tr>
<th>Tool</th>
<th>Percentage</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS/DIPSS</td>
<td>42%</td>
<td>5</td>
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<tr>
<td>DIPSS Plus</td>
<td>33%</td>
<td>4</td>
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<tr>
<td>I do not use a formal risk assessment tool</td>
<td>25%</td>
<td>3</td>
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<tr>
<td>MIPSS70/MIPSS70+ (V2.0)</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Total votes: 12</td>
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</tbody>
</table>

DIPSS, Dynamic International Prognostic Scoring System; MIPSS70, Mutation-Enhanced International Prognostic Scoring System 70; IPSS, International Prognostic Scoring System.

FLEISCHMAN: What do you think of the current risk-assessment tools?

DEKKER: Risk-assessment tools are more relevant for patients who [are younger], candidates for trials, transplant, etc. If you have an 80-year-old, whether they are low risk or very high risk, it will be dependent on what the patient wants, how far the patient is willing for you to go, and the other comorbidities.

FLEISCHMAN: I agree that the scoring tools are most helpful in a younger person for whom the transplant question is a reality. It seems like every year at ASH [American Society of Hematology Annual Meeting and Exposition], there are more of these prognostic scoring tools. We have a lot of scoring tools here.

CHAUDHARY: They also help you have a discussion with the patient about what we expect and what their prognosis looks like. I always calculate the score.

FLEISCHMAN: You are saying [that in the context of providing] help with patient education and for the patient...
to understand. I have had patients come in who found these scoring tools online, and they bring a printout with their scores. That is a rare circumstance I have encountered, but patients do find these things online and score themselves. Has anybody else had a patient come in scoring themselves?

SWEET: I have not, but...now that there is a proliferation of patient access to the medical records...they can look at their blood counts. They can probably even look at their pathology reports. You are right; this is likely to increase, but the patients are going to present us with all the data and ask us to elaborate.

DEKKER: I would somewhat agree. Probably 50% of phone calls or messages that I get from patients are, “I see my results in my chart; I do not know what it means. I am very anxious.” A few will do the research and go further, but most of the time they try to make an appointment between appointments.

CHANDURI: My experience is [initially] the patients may come 1 or 2 times [on their own]. The third time, usually, they come with their kids. When their son or daughter hears about myelofibrosis or some kind of blood disorder, that is when they will google it and they will bring all these things. Then they will ask, “Doctor, why are you not treating? Is it this? Is it that?” In the past year or so, I am finding this more. That is why it is better to give them all these tools up front.

FLEISCHMAN: Do you think increased patient education or access to information is a good thing?

CHANDURI: I think it is confusing for both. But it is happening, so we need to have a tool to communicate with these patients [explaining] if we are not going to treat them, why we are not treating.

Or if we are treating them, why are we treating? Because a lot of these medications are advertised on the television and then they will say, “Doctor, I have polycythemia vera [PV]; why are you not giving me this medication or that medication?” We need some tool because patients are coming in with this information.

FLEISCHMAN: I agree. I think in the United States, [individually] have the mentality: “If I have a disease and there is a treatment for it, I deserve this treatment for it.” But [it is important] to communicate with the patient exactly what a specific treatment can and cannot do—just because you have myelofibrosis does not mean you need a JAK [Janus kinase] inhibitor. Just because they are available does not mean that it is appropriate for the person.

DEKKER: But that is why all those agents are advertised online. When my son was 11, he came to me and told me about Neulasta [pegfilgrastim], because Neulasta was advertised in a YouTube video.

SWEET: There is a dichotomy of patients. There is still a large subset of patients in my practice who do not have the ability to get into the medical record or understand it. The patients who do a deep dive often focus on the wrong things....I do attempt to provide some education. Sometimes I find the brochures from the Leukemia & Lymphoma Society helpful to give the patient, once myelofibrosis is established, to give them a deep dive into their disease. I find the sections or subchapters in UpToDate that are relevant to the specific issue, like treatment of myelofibrosis. Something a little more focused, even though it is sophisticated reading, can be helpful in putting the patient more on a level of my choosing and not have them go all over the internet.

FLEISCHMAN: The National Comprehensive Cancer Network [NCCN] guidelines also have a patient version, which, for the myeloproliferative neoplasms [MPNs], is pretty good. It is mostly bullet points and pictures, and I think it covers things in good depth. Sometimes I look through the patient version when I want an answer to a question like “What do I do in this situation?” quickly. I am sure [individuals] can get that for free online, too. That is also a good source.

CHAUDHARY: I think providing background takes away anxiety from the patients....Giving them the tools such as “this is your score, this is your risk category, this is what we are going to do,” like a road map, helps take away that anxiety and future visits are easier.

SWEET: [Yes,] especially in diseases that do not necessarily have a clean bidimensional record of treatment response.

TALREJA: I agree, because some diseases have a clean-cut “do this, this, and this.” But in myelofibrosis, there [is no] clean-cut “do this and do that.” Some patients you watch forever. Some you give epoetin alfa [Procrit]. Sometimes you give ruxolitinib [Jakafi]. I do not think we should tell them so much about the disease; then they take that home and they come back and ask you, “Now, why aren’t you doing this?” It is so confusing for them.

FLEISCHMAN: Every patient is unique. For one person, a little information might be good for them, and they will stop asking you questions. Another person will ask more questions. The information is out there; if they want it, they can get it.
Now, say you have a [patient with] myelofibrosis; how often would you go back and peruse the NCCN guidelines to help with decision-making? How many of you have to look at the NCCN guidelines for MPNs?

DEKKER: Once, for sure.

SASTE: Once or twice a year. That is about it.

CHANDURI: Whenever there are new patients.

FLEISCHMAN: I am not sure how many versions there are, because it’s relatively recent that they have had NCCN guidelines. [The NCCN guidelines have been updated because of] pacritinib’s [Vonjo] recent FDA approval. For one patient with PV, when there was some discrepancy in terms of appropriate treatment, I pulled up the NCCN guidelines for PV in front of the patient and said, “This is where you are, and here is the [next step].” I think I have done that a few times.

CHAUDHARY: I had a patient who asked me to [check] JAK allelic burden every time she saw me.

FLEISCHMAN: Do any of you check JAK2 allele burden?

TALREJA: I do that to see whether it is going up, and getting better, and what is really happening to the disease—just out of curiosity, and it is interesting to see. Sometimes it is helpful and sometimes not at all.

I used to see hydroxyurea [Hydrea] reducing the JAK2 burden. But sometimes it did not, so I said, “All right, what am I going to do?”

FLEISCHMAN: How about other [individuals]? Do you check a JAK2 allelic burden at diagnosis, and then do you follow it?

TALREJA: Yes, I do follow it.

SASTE: I do not.

DEKKER: I have not.

CHAUDHARY: For those who ask for it, yes. Otherwise, I do not know.

FLEISCHMAN: I follow it if a patient is going on interferon. Many [patients] who go on interferon are very proactive, and they are doing it because they are hopeful that it is going to bring down their JAK2 allelic burden. In that case I say, “Let’s see where you are before you start the interferon and then let’s spot-check you after you have been on interferon for a while,” because that is their intention. They want to go on interferon for that purpose.

CHAUDHARY: That is exactly right. Most of my patients who ask for it are on interferon.

DISCUSSION QUESTIONS

FLEISCHMAN: In your practice, what is the trigger to initiate therapy for a patient with myelofibrosis? This question is focusing on JAK inhibitors.

SASTE: Symptomatic splenomegaly [is my primary trigger].

TALREJA: Abdominal pain, satiety, losing weight, discomfort, or the patient is getting progressively anemic and needs a change in treatment.

FLEISCHMAN: What about for that patient who may not necessarily have splenomegaly, [but] they were just picked up because they had some mild anemia; they would not have known it if somebody did not tell them that they were anemic, and they sort of stumbled on the diagnosis of myelofibrosis? Would you be enthusiastic about a JAK inhibitor in that person, or just let them be?

TALREJA: This patient was pretty anemic, hemoglobin was only 9.1 g/dL; if you put her on a JAK2 inhibitor, she is going to get more anemic.

FLEISCHMAN: The question is: Do they have other reasons to be on a JAK inhibitor, like [large spleen volume or being symptomatic]? But if they do not have those 2 issues, then [how would you treat]?

TALREJA: She was losing weight, and she had abdominal discomfort and things like that, but anemia was bad.

SWEET: The question, then: Is there a relevant role to treat in a presymptomatic phase? Because, as you alluded, the anemia is
Unless you are sure that the treatment you are giving [the patient] is going to be beneficial to change their disease trajectory, it is difficult to put somebody on a treatment that is going to make their current problem—anemia—worse.”

—ANGELA G. FLEISCHMAN, MD, PHD

likely to worsen. You can manage that with transfusion therapy. But is it more likely, in the scheme of things, to result in a better overall outcome by treating earlier in the disease course rather than one based on, historically, either symptomatic disease or whatever you define as rapidly changing counts?

FLEISCHMAN: I agree. What would…support that would be some secure data to say putting somebody on a JAK inhibitor will change their disease trajectory. That is [a difficult claim to make definitively] at this point. Unless you are sure that the treatment you are giving [the patient] is going to be beneficial to change their disease trajectory, it is difficult to put somebody on a treatment that is going to make their current problem—anemia—worse. Do you believe that a JAK inhibitor will alter the natural history of the disease?

TALREJA: No. JAK2 inhibition does not alter the pathophysiology or the bone marrow situation with myelofibrosis. It just improves the splenomegaly and they feel better, but I have never seen a JAK2 inhibitor change the physiology of the disease.

FLEISCHMAN: From my perspective, JAK2 inhibitors help with certain aspects of the disease, but I do not think we have clear-cut evidence that they change the disease physiology or trajectory.

BAGHIAN: I have never used it outside the indications, but I am always curious to know whether JAK2 inhibitors [affect] a patient’s hemoglobin in a beneficial way. Have you ever seen that?

TALREJA: I have never seen that.

FLEISCHMAN: I have seen, once or twice, in a post-PV patient who reverted slowly to their PV phase, who was having chronic inflammation that was contributing to their anemia; when I gave them the JAK inhibitor, it alleviated that. One patient asked, “Do you think I am going to need phlebotomies again?” But that was a single case. A second case was a patient who, at presentation, had a horrible gastrointestinal bleed. I think that is probably why he was anemic to begin with.

When do you consider clinical trial enrollment? Who do you send for clinical trials?

TALREJA: When you have exhausted all the treatments.

BAGHIAN: The poor-risk patients, for sure.

FLEISCHMAN: Do you feel the impetus for sending to the clinical trial is more the patient’s medical condition or personality—that they are asking for something else? How many times is it patient driven? Or you tell them, “Medically, this is very complicated and I do not have anything to offer; I think you need to go to a clinical trial.”

CHANDURI: I think since the cases are so few, and as a general practitioner I do not see them that often, I will refer them to a tertiary center where they are seeing more of these patients, at least for initial consultation, and then follow them. Because in our practices, we hardly see patients with myelofibrosis—only by diagnosis. I do not know about others. Unless they are running a completely hematology clinic, it is not a common disease that we all see.

CHAND: I agree. I think every patient should have access to clinical trials if there is one enrolling in the vicinity. We do not always have open enrolling trials, especially for these less common disease states. First line, second line, whatever it is, it is always good to have a patient go on a study if it is available locally.
FLEISCHMAN: How do [individuals] find clinical trials? Given that myelofibrosis is pretty rare, it is not like you are going to say, “Oh, I sent another patient for this trial last week.” What would you do, search clinicaltrials.gov, or what?

CHAND: I do search clinicaltrials.gov a lot. But sometimes there are places that reach out to you, especially if they have a trial that is open and enrolling. I have had providers reach out for rare diseases like paroxysmal nocturnal hemoglobinuria...where they are looking for patients. I generally keep that in mind when I see a patient with one of these rare hematologic conditions.

CHANDURI: I just send them to the tertiary center their insurance is contracted with. That way they will get a second opinion, and if they do not have any clinical trials with some kind of management treatment options, they will send them back to us and we can follow them. That is the way I think. I do not want to look for a trial for which they may or may not be eligible.

SASTE: I usually send them to City of Hope [Comprehensive Cancer Center in California]. That is our center.

BAGHIAN: I usually try to find someone I know who has an active laboratory in this field. It is hard [to find] someone such as yourself; or at UC San Diego Health [in California], I have Rafael Bejar, MD, PhD. I will ask him, “Do you have a clinical trial for this?” And if he says yes, then I will look for this.

FLEISCHMAN: Most [individuals] selected a JAK inhibitor plus referring for stem cell transplant. There was a long period when all we had was ruxolitinib, and then fedratinib came around, and pacritinib came around recently. Now we have more options for JAK inhibitors.

Does anybody want to say why they chose the JAK inhibitor that they did?

TALREJA: I chose pacritinib because the patient is already anemic. I do not want to make them [more] anemic. They are already in trouble. I have had problems with ruxolitinib and anemia—impossible to keep on transplant. I do not want to transfuse these patients, so I chose pacritinib because that is going to improve her anemia too, and not make her more anemic.

CHARU: I have a patient exactly like this right now, who is 70. I started him on ruxolitinib; even though he was anemic, he was also getting epoetin alfa, and he is going to get a transplant now. I am more used to ruxolitinib, so I just started him on that because he had a big spleen [From the Data].

FLEISCHMAN: That brings up the question of using something that you have been familiar with for the past decade, you know how to dose it, and you know what to expect with the drug vs using a new drug.

CHAND: I have had patients who have needed to be on epoetin alfa or epoetin alfa-epbx [Retacrit] just to help with the anemia. We have all used ruxolitinib for a long time. Because pacritinib is the newest kid on the block, I have not used it. I chose ruxolitinib because we have used hydroxyurea and then ruxolitinib; those have been the 2 most common drugs apart from best supportive care, transfusion, and epoetin alfa for these patients for a long time.

FROM THE DATA

In the COMFORT-I trial (NCT00952289), the rate of grade 3/4 anemia was 45.2% for those receiving ruxolitinib (n = 155) and 19.2% for those receiving placebo (n = 154). Approximately half of the grade 3/4 adverse events occurred in the first 8 weeks of treatment. Patients given ruxolitinib who had new-onset grade 3/4 anemia experienced an improvement in symptoms and reduction in their spleen volume, similar to patients who did not have anemia.
Have you ever used 2 agents in combination, like ESA [erythropoiesis-stimulating agents] and ruxolitinib at the same time?

FLEISCHMAN: I have in a few patients. With ESAs, mechanistically, it does not make sense why they should work in somebody who has a JAK2 V617F mutation, which should be turning on erythropoietin [EPO] signaling. What is more EPO going to do for them? But nevertheless, I have had patients on both. I can’t tell you how beneficial the EPO really was.

CHAND: The whole discussion about ruxolitinib and anemia—since you see more myelofibrosis than the rest of us do, what is your experience with anemia in these patients? How bad does it get? What do you tell your patients?

FLEISCHMAN: I would say I am very up-front with them to begin with. I heavily select patients who I think are appropriate for ruxolitinib, and I am clear that it may worsen their anemia. [Many] will say, “Thank you very much, but no, that is not for me.”

There is the type of person whose symptom burden is so horrible that they would rather need transfusions and feel good than be on the ruxolitinib. I have a few patients like that; they say, “I will gladly take these transfusions because it makes me feel better.” But for the majority of [individuals], if they do not have horrible symptom burden and they do not want to become more anemic, I would not start them on it in the first place.

TALREJA: I have had patients who were transfused every 3 to 4 weeks, and eventually became iron overloaded, and it was difficult.

FLEISCHMAN: In the setting of ruxolitinib?

TALREJA: No, even without ruxolitinib. Then I went to androgens, and I went to danazol. I went to interferon. I had to transfuse every 2 to 3 weeks.

FLEISCHMAN: Unfortunately, the anemic patient with myelofibrosis is admittedly a very frustrating patient; you can throw stuff at them, but you are going to be lucky if you do anything for their anemia. In my mind, the anemia in myelofibrosis is an unmet need, where there needs to be some improvement.

TALREJA: I agree with you. We need to take up anemia more than the splenomegaly, because I do not think the problem is the big spleen. The problem is truly fibrosis and anemia.

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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 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 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 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.

Fails — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® and 12% 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% (0.0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)
• Chemistry — In the TITAN study; hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study;
ERLEADA® + ADT demonstrated **SUPERIOR OS** in men with mCSPC vs ADT alone†-3

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

**HR=0.65; 95% CI: 0.53, 0.79**

- 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 months.†
- 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 months.‡

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hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1.0%); hypertriglyceridemia ERLEADA® 67% (1.6%), 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 rash (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 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

**Hypothyroidism** — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 15% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

**DRUG INTERACTIONS**

**Effect of Other Drugs on ERLEADA®**

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. However, reduce the ERLEADA® dose based on tolerability (see Dosage and Administration (2.2)).

**Effects of ERLEADA® on Other Drugs**

CYP3A4 is a strong inducer of CYP2C8 and CYP2C9, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C9, 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 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**

P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (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.

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**References:**

ERLEADA® (apalutamide) tablets

ADVERSE REACTIONS

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

- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

Clinical Trial Experience

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

The most common adverse reactions (‡10%) that occurred more frequently in the ERLEADA-treated patients (‡2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, 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 undergone 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), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2.3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (‡1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

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

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Condition (Organ/Class)</th>
<th>All Grades ERLEADA</th>
<th>Grade 3-4 ERLEADA</th>
<th>All Grades Placebo</th>
<th>Grade 3-4 Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>15</td>
<td>0.9</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Falls</td>
<td>6</td>
<td>0.6</td>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>Fractures</td>
<td>23</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>0</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>0.6</td>
<td>22</td>
<td>0.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0.4</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>0.2</td>
<td>9</td>
<td>0.2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flush</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Hot flush</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>Condition</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERLEADA N=524</td>
<td>Placebo N=527</td>
<td></td>
</tr>
<tr>
<td>Hematologic Abnormality</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td>Hyptertiglyceridemia</td>
<td>17</td>
<td>2.5</td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Chemistry</td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values
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Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

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

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3.2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most serious adverse reactions (>2%) were fracture (3.4%) in the ERLEADA arm and urinary retention (3.8%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients treated with ERLEADA and evaluate for loss of activity and at a Higher Incidence than Placebo (Between Arm Difference >5% All Grades) in SPARTAN (nmCRPC).

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and administration site conditions</td>
<td>39 1.4 28 0.3</td>
<td></td>
</tr>
<tr>
<td>Fatigue a,b,c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia a</td>
<td>16 0 8 0</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash a</td>
<td>25 5.2 6 0.3</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite a,b</td>
<td>12 0.1 9 0</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11 0 9 0</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall a</td>
<td>16 1.7 9 0.8</td>
<td></td>
</tr>
<tr>
<td>Fracture a</td>
<td>12 2.7 7 0.8</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>16 1.1 6 0.3</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 14 20 12</td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>14 0 9 0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 1.1 15 0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 0 16 0</td>
<td></td>
</tr>
</tbody>
</table>

a Includes fatigue and asthenia
b Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
c Includes rash, rash maculo-papular, 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
d Includes appetite disorder, decreased appetite, early satiety, and hypophagia
e 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), pruritus (6% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70 0.4 64 0.5</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47 0.3 29 0</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41 1.8 21 1.0</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia a</td>
<td>76 0.1 46 0</td>
<td></td>
</tr>
<tr>
<td>Hyperglyceremia b</td>
<td>70 2 59 1.0</td>
<td></td>
</tr>
<tr>
<td>Hypertiglyceridaemia c</td>
<td>67 1.6 49 0.8</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>32 1.9 22 0.5</td>
<td></td>
</tr>
</tbody>
</table>

a Does not reflect fasting values

Rash
In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism
In the combined data of two randomized, placebo-controlled clinical 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 treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 4.9% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted [see Drug Interactions].

Post-Marketing Experience
The following additional adverse reactions have been identified during post-approval use of ERLEADA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

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

Effect of Other Drugs on ERLEADA

CYP3A4, CYP2C9, CYP2C19, and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is not recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity [see Clinical Pharmacology (12.3) in Full Prescribing Information].
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P-gp, BCRP or OATP1B1 Substrates
Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/ OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
The safety and efficacy of ERLEADA have not been established in females. Based on 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 8-20). Findings included embryo-fetal lethality (resorptions) at doses ~50 mg/kg/day, decreased fetal anogenital distance, misshaped pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s), 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 years to 74 years, and 40% were 75 years and over. No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

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

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PATIENT COUNSELING INFORMATION
Advisie the patient to read the FDA-approved patient labeling (Patient Information).

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

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

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

Rash
• Inform patients that ERLEADA is associated with rash 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 for:
Janssen Products, LP
Horsham, PA 19044, USA
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In 2017, a Black man aged 55 years in a rural community received a diagnosis of hyperdiploid, Revised International Staging System (R-ISS) stage II multiple myeloma.

- Medical history: hypertension, controlled with lisinopril (Qbrelis)
- The patient received VRd (bortezomib [Velcade], lenalidomide [Revlimid], and dexamethasone) for 4 cycles, followed by autologous stem cell transplant (ASCT).
- The patient achieved a very good partial response (VGPR) and received lenalidomide maintenance, planned until progression.

After 3 years, the patient progressed and received daratumumab (Darzalex), pomalidomide (Pomalyst), and dexamethasone.

One year later:
- Laboratory results:
  - Hemoglobin: 11.5 g/dL
  - Calcium: 9.8 mg/dL
  - Creatinine: 1.1 mg/dL
  - Myeloma protein spike 1.4 g/dL (rising from nadir of 0.2 g/dL)
  - Rising light chain levels
- A PET scan showed new lytic lesions associated with hypermetabolic activity.
- Repeat bone marrow biopsy showed 60% plasma cells and 17p deletion in 50% of cells.

I think [many physicians] are becoming more familiar with BCMA-targeted therapy. [In the case of therapy with] an antibody-drug conjugate (ADC), the ADC is internalized; the linker is hydrolyzed, and the payload is released to cause cell death. [In the case of BCMA-targeted chimeric antigen receptor (CAR) T-cell therapy], CAR T cells binding to BCMA on the myeloma cell surface leads to CAR T-cell activation, cytotoxic cytokine release, and myeloma cell death. And finally, bispecific antibodies link BCMA on multiple myeloma cells and CD3 [on T cells], [triggering T-cell activation], release of cytotoxic cytokines, and then multiple myeloma cell death. So, BCMA is going to be an extraordinarily important target.

What therapies do the National Comprehensive Care Network (NCCN) guidelines recommend for patients who have received more than 3 prior therapies?

[It is important to note that] we’re coming into an era in which we have late relapses; that is, relapses in patients who have received more than 3 prior therapies. [According to the NCCN], after at least 4 prior therapies—including an anti-CD38 monoclonal [antibody], a proteasome inhibitor [PI], and an immunomodulatory drug [IMiD]—you could consider belantamab mafodotin [Blenrep], and you could consider idecabtagene vicleucel [ide-cel; Abecma] or

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Targeted Oncology™: What role does B-cell maturation antigen (BCMA) play in the pathogenesis and treatment of multiple myeloma?

RIFKIN: [This receptor] is highly expressed in normal and malignant plasma cells, and it’s on the surface of nearly all myeloma cell lines. Malignant plasma cells tend to have a lot more BCMA than do normal ones. Increased BCMA levels are associated with poorer outcomes, and upregulated expression during myeloma pathogenesis and evolution [progresses] from a normal [state to] monoclonal gammopathy of undetermined significance, then to smoldering multiple myeloma, and [finally to] active multiple myeloma.¹

What therapies do the National Comprehensive Care Network (NCCN) guidelines recommend for patients who have received more than 3 prior therapies?
ciltacabtagene autoleucel [cilta-cel; Carvykti]. For patients who have received more than 1 PI, more than 1 IMiD, and an anti-CD38 monoclonal antibody, you could consider selinexor [Xpovio] plus dexamethasone.²

What resources exist for choosing options after the second or subsequent lines of therapy?
The European Hematology Association and the European Society for Medical Oncology and the International Myeloma Working Group (IMWG)⁴ also offer guidelines for treating refractory or relapsed multiple myeloma (RRMM) after the second or subsequent line of therapy. [According to IMWG], when daratumumab, carfilzomib [Kyprolis], or elotuzumab [Empliciti] are not available, patients can receive [pomalidomide plus dexamethasone, with or without cyclophosphamide (Cytoxan)].

There are [also many] alternatives that have been approved, including selinexor, panobinostat [Farydak], oral PIs, and for slightly older patients, we can remember giving VdT-PACE [bortezomib, dexamethasone, and thalidomide (Thalomid), plus cisplatin, doxorubicin (Adriamycin), cyclophosphamide, and etoposide], which ended up landing a lot of patients in the hospital but was effective. Other investigational agents include, melphalan flufenamide [Pepaxto], BCMA-targeted agents [including CAR T cells and bispecific antibodies], and, for a small subset of patients, venetoclax [Venclexta]. Venetoclax is an option in patients who have translocation t(11;14) or high expression of BCL2.

CASE 1 UPDATE
• The patient asked about CAR T-cell therapy, but after counseling about its FDA indication, a referral was not made at this time.
• Belantamab mafodotin was initiated.
• Baseline ophthalmic examination (visual acuity [VA] and slit lamp ophthalmic eye exam) results were normal.

What data support the use of belantamab mafodotin for RRMM after 3 or more prior lines of therapy?
Those data come from the DREAMM-2 trial [NCT03525678]. In this trial, patients were treated until disease progression or unacceptable toxicity, with a primary outcome of overall response rate [ORR]. Secondary end points [included duration of response [DOR] as well as other efficacy outcomes and safety].

Patients had to have measurable disease, a decent performance status, and 3 or more [prior] lines of therapy. Also, patients had to be refractory and not [previously] exposed to a BCMA-targeted therapy. Prior ASCT was allowed; [allogeneic stem cell transplants were excluded].⁵ The baseline characteristics of the 2.5 mg/kg cohort show that it was a representative population. [The median] number of prior therapies [was 7]. The ISS stages I, II, and III [were represented by 22%, 34%, and 43% of the cohort, respectively].⁶

At the 13-month data cutoff, the ORR in this heavily pretreated population was about 32%. There were a few complete responses [CRs] and stringent CRs [5% and 2%, respectively], and a lot of stable disease [28%], PRs [13%], and VGPRs [11%]. This was not unexpected in this group. Responses did deepen over time. And [among patients with] high-risk cytogenetics or renal impairment, the response and survival outcomes were consistent with those of their [respective] populations. Not surprisingly, as we’re learning now, outcomes were poorer in patients with extramedullary disease.⁶

The most common adverse events [AEs] included keratopathy; significant cytopenias, a very rare infusion-related reaction; fatigue; and some neutropenia—a variety of things that were not totally unexpected.⁶

What are some considerations for managing keratopathy?
Considerations include how to best interact with your patient’s eye care provider, [implementation of] the Risk Evaluation and Mitigation Strategies program, the frequency of ophthalmologic examinations, and resources for managing ocular toxicity.

Keratopathy [can present] with or without symptoms. In the paper by Sagar Lonial, MD, [72% of patients in DREAMM-2] had any symptomatic or asymptomatic keratopathy, [56% of patients] were symptomatic, and [18% of patients] had VA changes. [Alternately, 82% of patients did not have] a clinically significant VA change. Discontinuation due to corneal AEs was not high [in 3% of patients]. There was 1 patient with a corneal ulcer.⁷

continued on page 18
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There is a significant warning about treatment-related corneal events [that arise from treatment with belantamab mafodotin]. Baseline examination is required, along with follow-ups. And you do have to delay treatment until improvement. You resume at [the same dose or at a] reduced dose, and you may even consider permanently discontinuing [treatment] based on severity.

In my experience, the patients will hold up the stop sign when they’re ready to stop. And [when treating], you should go through the available data [when advising patients]. We ask patients to use preservative-free lubricant eye drops 4 or more times a day. Contact lenses should only be used with [the supervision of] an ophthalmologist, and those can be corneal bandages. We do worry about [VA and] difficulty driving or operating machinery.

There are recommended dose modifications [for step-wise decreases in best corrected VA (BCVA)]. Importantly, when you get to [a BCVA of] grade 2 and beyond, you should start to withhold the belantamab mafodotin until the patient experiences an improvement in corneal findings and an [improvement in VA to grade 1 or less]. When the patient is at grade 4, you should [consider] permanent discontinuation, and [if you do continue treatment], you would require a substantial treatment delay. The interesting thing about this drug is it produces deep responses, and they can be long-lasting enough that you can spread out and reduce the dose of belantamab mafodotin.

**CASE 1 UPDATE**

- An increase in the frequency of preservative-free lubricant eye drop use was recommended.
- Dose 2 of belantamab mafodotin was delayed by 30 days until improvement to BCVA grade 1 in the right eye.
  - Treatment was resumed at 2.5 mg/kg.
- A VGPR was achieved after dose 2.
- The patient is continuing therapy.
  - Three additional treatment interruptions were needed due to corneal events of grade 2 to 3 (blurred vision, dry eyes, photophobia, and secondary elevation in the intraocular pressure managed with a topical pressure-lowering agent) with a dose reduction to 1.9 mg/kg.

**CASE 2**

- A woman aged 61 years was diagnosed with R-ISS stage III multiple myeloma (IgG-κ, high risk fluorescence in situ hybridization present).
- At the time, weekly VRd induction therapy was initiated.
- VRd was tolerated well with a best response of VGPR.
- She received an ASCT with complete remission and was placed on bortezomib-lenalidomide maintenance.
- She had elevated myeloma protein spike and new bony lesions 2 years later.
- Work-up confirmed disease progression.
- She was treated with carfilzomib/pomalidomide/dexamethasone; continued progression was noted after 16 cycles.
- She was enrolled in a clinical trial of an immunotherapy, with continued disease progression.
- Daratumumab-pomalidomide-dexamethasone was initiated.
- She received 2 cycles before disease progression was noted.
- The patient was referred to a CAR T-cell center and ultimately proceeded to CAR T-cell infusion.

**Targeted Oncology™: What data supported the approval of ide-cel, the first approved CAR T-cell therapy?**

**FORSBERG:** [That approval was based on the data from] the pivotal phase 2 KarMMa trial [NCT03361748]. This therapy was developed first by bluebird bio, then Celgene. This was studied in a heavily pretreated patient population [in which patients had received] more than 3 prior lines of therapy, including a prior IMiD, a PI, and an anti-CD38 therapy; this shaped the approval indication.

These patients were treated with 3 days of lymphodepleting chemotherapy, which was fludarabine and cyclophosphamide, on days −5, −4, and −3, which is a standard lymphodepletion approach. Then, patients were infused with the CAR T cells that had been manufactured, [a process requiring] about a month. There was a range of cell doses that patients received, and the primary end point was ORR.

It is notable that [the tumor response] was cell dose dependent. The relatively small number of patients who got a modest dose of $150 \times 10^6$ CAR T cells had an ORR of about 50%. In the larger group of patients who got...
300 × 10^6 cells, the ORR was about 70%, and in the patients who got 450 × 10^6 [cells], the ORR was 81%. So, predictability of those cell yields is a bit harder to achieve, but it did impact how deep the ORR was and how many patients achieved things like VGPR, CR, or better.\textsuperscript{11}

Cell dose also impacted how durable the responses were. Not surprisingly, patients who got deeper responses had more durable responses. Patients who achieved a VGPR had a median DOR of [10.4 months; 95% CI, 5.1–11.3]. The median DOR was [19.0 months; 95% CI, 11.3–not estimable (NE)] in patients with a CR. For patients who only achieved a PR, the median DOR was only 4.5 months [95% CI, 2.9–6.7], which is suboptimal.\textsuperscript{11}

In patients who got the highest cell dose, 450 × 10^6, the median progression-free survival [PFS] was [12.1 months; 95% CI, 8.8–12.3] vs only [5.8 months; 95% CI, 4.2–8.9] in the 300 × 10^6 cell-dose group, and only [2.8 months; 95% CI, 1.0–NE] in the 150 × 10^6 cell-dose group. So, for patients who got a suboptimal cell dose, and who got a suboptimal response, those remissions ended up not being all that durable, whereas if patients got a better cell dose and a better depth of response, they did have more stable remission. We see that essentially all patients have demonstrated progression on this KarMMa trial of ide-cel in relapsed, heavily pretreated patients.\textsuperscript{11}

The [toxicity profile in this trial includes] the AEs you think about most often when we’re thinking of a CAR T-cell therapy, such as cytokine release syndrome [CRS]. When I counsel patients, I tell them that they’re almost assuredly going to get CRS. In this trial, 84% of patients had CRS, and only 5% of patients had CRS of grade 3 or 4. So, we don’t [see] much high-grade or life-threatening CRS. Neurotoxic effects occurred at a relatively low rate.

This [consisted mostly of] classical immune effector cell–associated neurotoxicity syndrome [ICANS], the type of neurotoxicity that is most characterized with CAR T-cell therapy. About 18% of patients experienced neurotoxic effects of any grade, and about 3% had neurotoxic effects of grade 3 or higher. Some of the other AEs that we commonly see include higher-grade myelosuppression in the setting of the lymphodepleting chemotherapy that the patients receive.\textsuperscript{11}

What data supported the subsequent approval of cilta-cel CAR T-cell therapy?

Both [ide-cel\textsuperscript{10} and cilta-cel\textsuperscript{12}] were approved based on single-arm phase 2 trials. [Cilta-cel was approved based on the phase 1b/2 CARTITUDE-1 study [NCT03548207].\textsuperscript{12} CARTITUDE-1 was similar in design to KarMMa; patients needed to have received 3 or more prior lines of therapy, including a prior PI, an IMiD, and an anti-CD38 monoclonal antibody.

The patients went through similar apheresis, followed by bridging as needed; neither of the studies mandated bridging therapy. Then, patients received fludarabine and cyclophosphamide lymphodepletion, and then cell infusion. [There was a] lower potential cell-dose target with cilta-cel, and similar structured follow-up.\textsuperscript{11,13,14}

In both [KarMMa and CARTITUDE-1, the patients] were heavily pretreated. [In CARTITUDE-1], the patients had received a median of 6 prior lines of therapy. Most of these patients [66%] had greater than 5 prior lines of therapy, [87.6%] were triple-class refractory, and [42.3%] were penta-drug refractory, meaning they were refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab. And unfortunately, as in many of these CAR T-cell trials, Black patients were underrepresented, which has been an unfortunate characteristic of a lot of these studies. A decent number of patients, [13.4%] had extramedullary disease. [This was a smaller percentage] than in KarMMa, which physicians sometimes point to [as a cause] of the difference between the activity profiles [of the respective therapies], but it’s hard to say [whether that is truly a cause].\textsuperscript{11,14}

![FIGURE. Best Response to Cilta-cel in the CARTITUDE-1 Trial\textsuperscript{14}](image)

<table>
<thead>
<tr>
<th>Best response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>3.1%</td>
</tr>
<tr>
<td>VGPR</td>
<td>12.4%</td>
</tr>
<tr>
<td>PR</td>
<td>82.5%</td>
</tr>
</tbody>
</table>

PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
The efficacy profile that we have to date is from the American Society of Hematology Annual Meeting and Exposition in 2021 [Figure 1]. The ORR was [97.9%], and a robust percentage of patients achieved a CR or better: 82.5% achieved stringent CR, and [94.9%] achieved VGPR or better. Median DOR has not yet been achieved. As with most CAR T-cell profiles in myeloma, the [median] time to first response was brisk [1 month; range, 0.9-10.7]. The median time to best response [2.6 months; range, 0.9-17.8] is probably a [reflection] of how long it takes to clear out [the] paraprotein in the blood. Marrow responses are even faster than what you see in the blood; these patients often get their deepest response in the marrow quickly.

The survival [data are] a little different, [in my opinion], from what we saw with KarMMa. After a 2-year median follow-up, the median PFS with cilti-cel [had not been reached], unlike ide-cel, which produced a median PFS in the 8-month to 10-month range. With cilti-cel, [60.5%] of patients had not progressed [at 2 years]. And, in patients who achieved a deeper response, including the large portion of patients who achieved minimal residual disease negativity [92%], the response was even more durable. So, cilti-cel [produced] impressive DOR and depth of response.

There were many different toxicities associated [with this treatment]; high-grade hematologic toxicities were common. Recovery from this is much [closer to] what you’d see with regular semi-intensive chemotherapy, [rather than] what we see with myeloablative conditioning for transplant or even some infusional intensive chemotherapy with Vdt-PACE and [similar regimens]. CRS was, again, experienced by 95% of patients, but [there was] a very low percentage of CRS events of grade 3 or higher [4%].

A different neurotoxicity profile is one of the important things to note about the CARTITUDE-I data vs the KarMMa data. In CARTITUDE-I, 21% of patients experienced neurotoxicity, and 9% had high-grade neurotoxicity. This [neurotoxicity] included both ICANS, the classical CAR T-cell–associated toxicity, as well as some other neurotoxicities, which included neurocognitive and kinetic issues in about 12 patients.

REFERENCES
had diastolic blood pressure ≥ 3). Systolic blood pressure hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), thromboembolic event within the previous 6 months. Withhold and resume at reduced dose upon recovery 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.

**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**
**Warnings and Precautions**
**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.

**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.

**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.

**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.

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

• 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])

— 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm

**See a spectrum of results**
Let LENVIMA® change the way you view treatment in second-line advanced RCC.
14.6-month median PFS: with LENVIMA + everolimus vs everolimus alone\(^1\)

![Graph showing median PFS](image)

- 26 events (51\%) occurred in the LENVIMA + everolimus arm vs 37 events (74\%) in the everolimus arm\(^1\)
  - 21 patients (41\%) who received LENVIMA + everolimus progressed vs 35 patients (70\%) who received everolimus
  - Death occurred in 5 patients (10\%) who received LENVIMA + everolimus vs 2 patients (4\%) who received everolimus

- 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\(^1\)

- 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 (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 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\(^1\)

\(^{RCC}=\)renal cell carcinoma; \(^{PFS}=\)progression-free survival; \(^{TKI}=\)tyrosine kinase inhibitor; \(^{CI}=\)confidence interval; \(^{HR}=\)hazard ratio.

### 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, 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 QT 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 (lenvatinib) capsules 10 mg and 4 mg

Please see all Selected Safety Information throughout and accompanying brief summary of full prescribing information.
SELECTED SAFETY INFORMATION

Warnings and Precautions (cont’d)

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 8% 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 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 were diarrhea (21%), fatigue (6%), thrombocytopenia (6%), vomiting (6%), nausea (6%), and proteinuria (5%). 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 RCC 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 with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and 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).

Renal Cell Carcinoma (RCC)

• 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)

• For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

Endometrial Carcinoma (EC)

• In combination with pembrolizumab, for the treatment of patients with advanced endometrioidal carcinoma (EC) that is not microsatellite instability-low (MSI-L) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

DOSE AND ADMINISTRATION

Important Dosage Information

• Reduce the dose for certain patients with renal or hepatic impairment. Take LENVIMA once daily, with or without food, at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

Single Agent Therapy:

• DTC: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg

• RCC: The recommended dosage is 24 mg orally once daily.

• EC: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

• HCC: The recommended dosage is based on actual body weight: 12 mg orally once daily for patients greater than or equal to 60 kg or 8 mg orally once daily for patients less than 60 kg.

Combination Therapy:

• The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

• HCC: The recommended dosage is 16 mg orally once daily with everolimus 5 mg orally once daily.

Dose Modifications for Adverse Reactions: Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. It lists the dose modifications for several different conditions.

Table 1. Recommended Dose 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 optimal antihypertensive therapy. Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.</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. Resume at a reduced dose or discontinuation depending on severity and persistence of adverse reaction.</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. Resume at a reduced dose or discontinuation depending on severity and persistence of adverse reaction.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Renal Failure or Impairment</td>
<td>Grade 3 or 4</td>
<td>Withhold until improves to Grade 0 or 1 or baseline. Resume at a reduced dose or discontinuation depending on severity and persistence of renal impairment.</td>
</tr>
<tr>
<td>Proteinaemia</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. Resume at a reduced dose. 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 improves to less than or equal to 483 mmHg or baseline. Resume at a reduced dose.</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Greater than 500 ms or greater than 60 ms increase from baseline</td>
<td>Withhold until fully resolved. Resume at a reduced dose or discontinuation depending on severity and persistence of neurologic symptoms.</td>
</tr>
<tr>
<td>Reversible Posterior Leukoencephalopathy Syndrome</td>
<td>Any Grade</td>
<td>Withhold until improves to Grade 0 or 1 or baseline. Resume at a reduced dose.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Persistent or intolerable</td>
<td>Withhold until improves to Grade 0 or 1 or baseline. Resume at a reduced dose.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 laboratory abnormality</td>
<td>Permanently discontinue.</td>
</tr>
</tbody>
</table>

Dose Modifications for Severe Renal Impairment

The recommended dosage of LENVIMA for patients with DTC, HCC, or endometrial carcinoma and severe renal impairment (creatinine clearance less than 30 ml/min calculated by Cockcroft-Gault equation using actual body weight) is:

- 8 mg once daily in combination with pembrolizumab 200 mg
- 4 mg once daily in combination with pembrolizumab 100 mg

Dose Modifications for Severe Hepatic Impairment

The recommended dosage of LENVIMA for patients with DTC, HCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is:

- 4 mg once daily
- 2 mg once daily

PRECAUTIONS

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. The median time to onset of new or worsening hypertension was 14 and 26 days, respectively, in SELECT and REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% of REFLECT. Grade 4 hypertension occurred in 1% of SELECT and Grade 4 hypertension was not reported in REFLECT. In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 or 4 hypertension occurred in 13% of patients. Systolic or diastolic blood pressure greater than or equal to 160 mmHg or 100 mmHg occurred in 21% of patients and diastolic blood pressure greater than or equal to 90 mmHg occurred in 7% of patients. 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 2 months, and then at least monthly thereafter during treatment. Withhold and resume 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 789 patients with DTC, RCC, or HCC, Grade 2 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, cardiac failure due to cerebral or peripheral embolization, or cardiac failure due to cerebral or peripheral embolization) occurred in 8% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Arterial Thromboembolic Events

Among patients receiving LENVIMA with everolimus, arterial thromboembolic events (ATE) occurred in 5% of patients. The incidence of arterial thromboembolic events in patients receiving LENVIMA with pembrolizumab, arterial thromboembolic events were noted in 5% of patients in CLEAR, 4% in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 or 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, arterial thromboembolic events in any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%). Permanently discontinue LENVIMA following an arterial thromboembolic event. The safety of resuming LENVIMA 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 1372 LENVIMA-treated patients with malignancies other than RCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatic apoplexy, occurred in 0.5% of patients. In SELECT (HCC), hepatic encephalopathy (including hepatic encephalopathy, hepatic encephalopathy, metabolic encephalopathy, and hepatic encephalopathy) occurred in 8% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of LENVIMA-treated patients and 2% of sorafenib-treated patients. Grade 3 to 5 hepatic failure occurred in 3% of LENVIMA-treated patients and 5% of sorafenib-treated patients. Two percent of patients discontinued LENVIMA and 0.2% discontinued sorafenib due to hepatic encephalopathy and/or hepatic failure. Permanently discontinue LENVIMA if Grade 3 or 4 hepatic failure occurs. 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 HCC closely for signs of hepatic dysfunction, including hepatic encephalopathy. Withhold and resume at a reduced dose or permanently discontinue LENVIMA based on severity.

Renal Failure or Impairment

Serious, including 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% totally in each study. In Study 205 (RCC), renal impairment or failure occurred in 18% of patients receiving LENVIMA with everolimus, including Grade 3 in 10% of patients. Initiate prompt management of diabetes or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA for renal failure or impairment 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% of patients in SELECT (DTC) and 3% proteinuria occurred in 8% of patients in REFLECT (HCC), respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA with pembrolizumab 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 3+ is detected, obtain 24-hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

Diabetes

Of the 737 patients treated with LENVIMA in SELECT (DTC) and REFLECT (HCC), diabetes occurred in 40% of patients, including Grade 3 diabetes in 6%. In Study 205 (RCC), diabetes occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 in 19%. Diabetes was the most frequent cause of dose interruption/reduction and diabetes required dose reduction.

*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 (2:1:1 to LENVIMA vs placebo [N=281] or placebo [N=131]). The median treatment duration was 16.1 months for LENVIMA. Among 281 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, diastolic or systolic hypertension, palpitations, headache, weight gain, fatigue, nausea, vomiting, diarrhea, dyspepsia, and dysphonia. The most common serious adverse reactions (at least 2%) were hypertension (3%), hypothyroidism (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA. One patient discontinued LENVIMA due to adverse reactions leading to dose reductions.

The following tables present adverse reactions occurring at a higher rate in LENVIMA-treated patients than those receiving placebo.

### Table 3: Adverse Reactions in Patients with a Betweengroup Difference of ≥5% in All Grades or ≥2% in Grades 3 and 4 in SELECT (DTC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 24 mg N=250</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Oral pain</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis/Myalgia</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>Increased weight</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>Increased weight</td>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td><strong>Laboratory Abnormalities in SELECT (DTC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Abnormality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (AST)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Increased alanine aminotransferase (ALT)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypocalcemia</strong></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperkalemia</strong></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (AST)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Increased alanine aminotransferase (ALT)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Laboratory Abnormalities in SELECT (DTC)

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: hypocalcemia, increased alkaline phosphatase, hypomagnesemia, hypocalcemia, hyperbilirubinemia, hypercalcinemia, hypercholesterolemia, increased serum amylose, and hyperkalemia.
First-Line Treatment of Renal Cell Carcinoma in Combination with Pembrolizumab (CLEAR)  

The safety of LENVIMA in combination with pembrolizumab was investigated in CLEAR (see Clinical Studies [42]). pembrolizumab in combination with LENVIMA was administered 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks (n=350), or pembrolizumab 200 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=386). The median duration of exposure to the combination therapy of LENVIMA and pembrolizumab was 17 months (range 0.1-38).

Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA in combination with pembrolizumab, including cardiac-arrest respiratory arrest (0.3%), sepsis (0.3%), and one case (0.3%) each of asthmatic, autoimmune hepatitis, chest pain, delirium, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonia, ruptured aneurysm and subarachnoid hemorrhage. Serious adverse reactions occurred in 51% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in <2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), musculoskeletal and connective tissue disorders (3%), musculoskeletal chest pain (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 37% of patients. 20% LENVIMA only, 29% pembrolizumab only, and 15% both drugs. The most common adverse reactions (≥2%) leading to permanent discontinuation of LENVIMA, pembrolizumab, or both were present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, Graves ophthalmopathy, hepatic failure, hypertension, increased blood creatinine, multiple organ dysfunction syndrome, proteinuria, renal failure, and urinary infection. The most common serious adverse reactions (≥5%) observed in the LENVIMA with pembrolizumab-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (6%), dyspnea (6%), decreased appetite (5%), and dehydration (5%). The most common serious adverse reactions (≥30%) observed in the LENVIMA with everolimus-treated group were diarrhea (29%), fatigue (10%), thrombocytopenia (6%), increased blood creatinine (5%), nausea (5%), vomiting (5%), decreased appetite (5%), and dehydration (5%).

Grades 3 and 4 increased ALT or AST was seen in 5% of patients. Grade 3-4 hypertension was observed in 14% (18% patients); reduction or discontinuation of any of the 2 drugs was not designed to demonstrate a statistically significant difference in adverse reaction rates for LENVIMA with pembrolizumab versus everolimus.

Treatment discontinuation due to an adverse reaction occurred in 29% of patients receiving LENVIMA in combination with pembrolizumab. The most common adverse reactions observed in the LENVIMA with everolimus-treated group (≥30%) were in order of decreasing frequency: diabetes, fatigue, arthritis/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, diaphoresis, rash, decreased weight, and proteinuria. The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (8%), thrombocytopenia (8%), diarrhea (8%), vomiting (5%), and dehydration (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA with everolimus. The most common adverse reactions (≥5%) resulting in dose reductions in the LENVIMA with everolimus-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (8%), vomiting (8%), nausea (8%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA with everolimus-treated group.

Table 7 presents the adverse reactions in >15% of patients in the LENVIMA with everolimus arm. Study 205 was not designed to demonstrate a statistically significant difference in adverse reaction rates for LENVIMA with pembrolizumab versus everolimus, as compared to the baseline laboratory measurement for each parameter. LENVIMA/pembrolizumab (n=343 to 348) and pembrolizumab (n=229 to 235).

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LENVIMA 20 mg in combination with Pembrolizumab 200 mg (n=352)</th>
<th>pembrolizumab (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td><strong>All Grades (%)</strong></td>
<td><strong>Grades 3-4 (%)</strong></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal bowel habit</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>57</td>
<td>3</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>56</td>
<td>29</td>
</tr>
<tr>
<td>Hemorrhagic event</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased amylase</td>
<td>61</td>
<td>17</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td><strong>Reproductive system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td><strong>Hematopoietic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>1</td>
</tr>
</tbody>
</table>

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 20 mg in combination with Pembrolizumab 200 mg (n=352)</th>
<th>pembrolizumab (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>Increased lactate dehydrogenase</td>
<td>61</td>
<td>34</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase/AST</td>
<td>57</td>
<td>5</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>55</td>
<td>7</td>
</tr>
<tr>
<td>Increased alanine aminotransferase/ALT</td>
<td>54</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Nephromegaly</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
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<td>4</td>
</tr>
<tr>
<td>Heparinophilia</td>
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<td>7</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
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<td>2</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
<td>9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 7: Adverse Reactions Occurring in >5% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LENVIMA 18 mg with Everolimus 5 mg (n=62)</th>
<th>Everolimus 5 mg (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>54</td>
<td>3</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>55</td>
<td>5</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 (RCC)

<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</td>
<td>8</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Medialiastial</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Dyspnea/Eosinophil dyspepsia</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension/Increased blood pressure</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>32</td>
<td>6</td>
</tr>
</tbody>
</table>
| Hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%). Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group.

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

<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 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Increased Eosinopenia</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

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 Sorafenib 800 mg N=476</th>
<th>Sorafenib 400 mg N=476</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>Renal failure event</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>14</td>
</tr>
</tbody>
</table>

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

<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>13</td>
<td>20</td>
</tr>
<tr>
<td>Hypoalbumin</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Endometrial Carcinoma
The safety of LENVIMA in combination with pembrolizumab was investigated in Study 369, 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 settings. 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 (n=342), or received durvalumab or placebo (n=329).

For patients with not MSI-H or dMMR status, the median duration of study treatment was 7.2 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 LENVIMA-treated patients were hypertension (8%), fatigue (5%), decreased appetite (4%), and anorexia (4%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of LENVIMA were fatigue (8%), increased aspartate aminotransferase (ALT), diarrhea (8%), proteinuria (7%), hypokalemia (7%), and palmar-plantar erythrodysesthesia syndrome (5%). Treatment discontinuation due to adverse reactions occurred in 26% of patients in the LENVIMA-treated group.

Adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), anemia (11%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%). Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of these patients. The most common (>1%) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), anemia (11%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%).
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 (7%), 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 (≥2%) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (8%), decreased appetite (5%), vomiting (5%), increased alkaline phosphatase (5.5%), fatigue (5.5%), nausea (5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), and proteinuria (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 11: Adverse Reactions in ≥20% of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

<table>
<thead>
<tr>
<th>Endometrial Carcinoma (not MSI-H or dMMR)</th>
<th>LENVIMA 20 mg in combination with Pembrolizumab N=342</th>
<th>Pembrolizumab or Paclitaxel N=255</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>All Grades* (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>67</td>
<td>0.9</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37</td>
<td>2.3</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>35</td>
<td>2.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>2.6</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia*</td>
<td>23</td>
<td>2.9</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* Graded per NCI CTCAE v4.03

### 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)

<table>
<thead>
<tr>
<th>Endometrial Carcinoma (not MSI-H or dMMR)</th>
<th>LENVIMA 20 mg in combination with Pembrolizumab N=342</th>
<th>Pembrolizumab or Paclitaxel N=255</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Test</td>
<td>All Grades* (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Laboratory Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>60</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>58</td>
<td>9</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>53</td>
<td>3.2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>Increased alkaline phosphate</td>
<td>43</td>
<td>4.7</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>40</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* With at least 1 grade increase from baseline

### 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

### Hematology

- Hepatobiliary: cholestasis
- Renal and Urinary: nephrotic syndrome

### Vascular

- arterial (including aortic) 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 obvious adverse changes at doses up to the recommended human dose; however, decreases in body weight and reductions in food consumption were observed in pregnant rats and rabbits. There are no available animal data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

#### 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 rabbits during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.3 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA).
- Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail) visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.01 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 1/3 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).

**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**

- Following administration of radioabeled/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.

**Pediatric 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 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth 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.
Geriatric Use Of the 261 patients with differentiated thyroid cancer (DTC) who received LENVIMA in SELECT, 45% 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 pembrolizumab 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, 36% 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.

Renal Impairment 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.

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Examining Treatment Options for Second-Line ES-SCLC Therapy

**CASE**

- A 58-year-old, moderately active man presented with worsening shortness of breath, persistent dry cough, and fatigue.
- Medical history: smoker with a 30 pack-year history
- ECOG performance status: 1
- Chest x-ray showed opacity in left lung.
- Chest CT showed a hilar mass, with invasion of the left pulmonary artery and 3 contralateral lung nodules present.
- Brain MRI: negative
- Bronchoscopy with transbronchial biopsy/pathology: small cell lung cancer (SCLC)
- Diagnosis: extensive-stage SCLC (ES-SCLC)

- He received 4 cycles of carboplatin, etoposide, and atezolizumab (Tecentriq).
- He initially achieved a partial response.
- Seven months after the last cycle of platinum chemotherapy, shortness of breath returned, with right upper quadrant pain and midback pain.
- CT of chest, abdomen, and pelvis showed hematogenous metastases in the liver and adrenal glands.
- Imaging: negative for brain metastases
- Laboratory results: within normal limits
- ECOG performance status: 1

**POLLING QUESTION**

At a live virtual event, Santana-Davila asked participants, “What would you most likely recommend for this patient outside a clinical trial?”

- Platinum rechallenge 55% (6)
- Lurbinectedin 36% (4)
- Topotecan 9% (1)
- Other single-agent chemotherapy 0% (0)
- Cyclophosphamide, doxorubicin, and vincristine 0% (0)
- Other 0% (0)

Total votes: 11

**Targeted Oncology™: What is the recommended second-line therapy for ES-SCLC?**

**SANTANA-DAVILA:** The National Comprehensive Cancer Network [NCCN] guidelines on SCLC recommend that if the relapse occurs within 6 months, the options are either oral or intravenous (IV) topotecan, lurbinectedin [Zepzelca], or a clinical trial.1 [Other recommended regimens are] taxanes, irinotecan [Camptosar], temozolomide [Temodar] in the presence of brain disease especially, and CAV [cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin)] chemotherapy.

Bendamustine [Treanda] is category 2B because it showed some activity in a clinical trial. In patients who have relapsed for more than 6 months after initial therapy, the recommendation is to give the original regimen. Lurbinectedin is the only drug that has been approved [recently], and this was in June 2020.2

**What data support a platinum rechallenge?**

The NCCN panel recommends rechallenge for relapse after 6 months [from treatment]. There’s another study that was published in *Lancet* in 2020.3 This was a French study. In France, and Europe in general, they use 90 days to define platinum sensitivity, and this was a study where patients with SCLC who have progressed at least 90 days [after completion of first-line treatment] were [randomly assigned] to topotecan or platinum rechallenge. Interestingly, the median progression-free survival [PFS] was better in patients who were rechallenged with platinum at 4.7 months vs 2.7 months in patients treated with topotecan [HR, 0.57; 90% CI, 0.41-0.73; P = .0041].3

There was a larger overall response rate [ORR] difference. It was 49% for platinum therapy vs 25% for topotecan [P = .0024]. Interestingly though, it’s not clear that overall
survival [OS] was changed. But if we look at the trial, up to one-third of patients who were [randomly assigned] to topotecan went on to receive third-line platinum rechallenge. One might suspect that is the reason why they did not show an OS advantage.³

In my practice, if a patient had a decent tolerance to a platinum challenge and it’s been more than 3 months, based on these data, I consider rechallenging with the same platinum agent. I typically use a platinum and a taxane, just because there’s nothing magical about etoposide for this traditionally. My idea is because this is platinum rechallenge, it is best to introduce a second agent that tends to be as equally tolerated as etoposide without having them come [to the clinic] for a few days straight. I typically do that as a standard in patients that have a platinum rechallenge after 90 days. A lot has to do with how they tolerate treatment and what their goals are. If the platinum rechallenge beats them up, I tend to go to a single agent. So to me these goals are obviously important.

**Why is immuno-oncology (IO) not considered an option for these patients, considering data showing efficacy of ipilimumab (Yervoy) and nivolumab (Opdivo)?**

If patients relapse while on maintenance IO, I think that they’ve proven that it does not work, and I do not rechallenge them. Back before the era of immuno-therapy, there was [the CheckMate 032] phase 1/2 study [NCT01928394] that showed patients who had progressive disease after chemotherapy who were treated with ipilimumab or nivolumab. [Some cohorts were] nonrandomized.

Some patients were treated with nivolumab alone. Some patients were treated with high-dose ipilimumab at 3 mg/m² and low-dose nivolumab at 1 mg/m², and the other way around. They found that patients who were treated with 3 mg of ipilimumab and 1 mg of nivolumab had a 22% response rate.⁴ Because of that, the NCCN endorsed that regimen, which lived for a little bit. Then came the atezolizumab and durvalumab [Imfinzi] data, and there was no reason to put patients on ipilimumab or nivolumab if they had already had exposure to immunotherapy.

Then there were 2 clinical trials that were done, 1 in the maintenance setting [NCT01450761] where patients were treated with a platinum-based agent and etoposide. After the 4 cycles, they were randomly assigned to etoposide alone vs etoposide and ipilimumab, which did not show any evidence of improvement in OS for the patients on ipilimumab.⁵

But it did [result in] toxicity, and this was a higher-dose ipilimumab, [10 mg/kg, which] was significant. The incidence of colitis was high. Similarly, there was another study [CheckMate 451; NCT02538666] that was a phase 3 study where patients on second-line therapy who were immunotherapy naive were randomly assigned to ipilimumab and nivolumab vs nivolumab alone [vs placebo]. There was no evidence of improvement in OS.⁶ It’s difficult to know why this was the case and why we saw an improvement before, but based on those data, the NCCN decided to not endorse this regimen anymore. I’ve had a couple of patients that are 3 and 5 years out from ipilimumab plus nivolumab when we could do that, and the disease is under control. Were we just lucky? Does ipilimumab have anything to do with it? We don’t know, but unfortunately, we don’t have a role for ipilimumab and nivolumab outside a clinical trial setting.

I would not use [nivolumab and ipilimumab]. I am biased because thankfully I have access to clinical trials. When my patients are on third-line therapy, I would not use it, and I would not recommend it. Is it wrong to use it? No, I don’t think so, but do the data support it? No, they do not.

**What data support the use of lurbinectedin for SCLC after progressing with chemotherapy?**

Lurbinectedin was approved based on a phase 2 basket study [NCT02454972].² It’s an interesting story. Lurbinectedin comes from a Spanish company called PharmaMar, [which was] looking at different compounds that were researched at sea and...developed lurbinectedin as one of those compounds. [PharmaMar] first started [lurbinectedin] in a large phase 1 study [NCT01980667] and noticed that a few patients with SCLC responded, so [it] did the basket study using the maximum tolerated dose of lurbinectedin at 3.2 mg/m² IV every 3 weeks. [It] also did the ATLANTIS study [NCT02566993], which is a phase 3 study of lurbinectedin. [PharmaMar] didn’t think that lurbinectedin alone would control the disease, so [it] used lurbinectedin and doxorubicin compared with topotecan or CAV, which is commonly used in Europe. [It] did these 2 studies in parallel.

The basket study was presented first at the 2018 American Society of Clinical Oncology Annual Meeting and was later published in *Lancet* in 2020.³ It was a single-arm study in patients that had an ECOG performance score of 0 to 2 and prior chemotherapy exposure. Prior immunotherapy was allowed; it was still not the standard of care. Patients with CNS [central nervous system] metastases were excluded, and the primary end point was the ORR. The null hypothesis was a 15% or less response, and the alternative hypothesis was a response of more than 30%.⁷

So 105 patients were treated with this regimen, more men than women—as is seen in the disease commonly. The median age was 60. Most patients had an ECOG status of 0 or 1. 42% did not. Most were smokers, as you might expect. CNS involvement was present in 4%. Again, they did not have active brain metastases. Patients who had treated brain metastases were allowed. For prior therapies, platinum...
was used in 100% of the cases, etoposide in 99%, IO in 8%, and PARP inhibitors in 2%. The important thing to note is IO is only in 8% of the cases. That is because this was not the standard of care then. Prior response to platinum was what we would expect. The majority of patients had a partial response at 67%. Complete response [CR] was 9%, and stable disease [SD] was 18%. Forty-three percent of patients had a median chemotherapy-free interval [CTFI] of less than 90 days, and 57% of patients had a CTFI of more than 90 days.7

**What was the efficacy seen in this trial?**

In all patients, the ORR was 35.2% [95% CI, 26.2%-45.2%]. There were no CRs, and 33% had SD [for at least] 3 months.7 Progressive disease was present in 27% of the patients. The disease control rate was 68.6%, and the median duration of response was 5.3 months, with 43% of patients still responding at 6 months. The median follow-up was 17.1 months.

Patients who had a CTFI of less than 90 days obviously had worse and more aggressive disease [Table]. The median PFS in these patients was 2.6 months vs 1.6 months in those who had an interval of more than 90 days. The 4-month PFS rate was 29.1% in the less-than-90-days [CTFI] group vs 59.9% in the more-than-90-days [CTFI] group. The 6-month PFS rate was 18.8% in the less-than-90-days group vs 43.5% in the more-than-90-days group. The median OS was 5.0 months in the less-than-90-days group vs 11.9 months in the more-than-90-days CTFI group.

The 12-month OS rate was 15.9% in the less-than-90-days group vs 48.3% in the more-than-90-days group. The ORR in patients with more than 90 days CTFI was 45%, and in patients with more than 180 days, CTFI was 60%.8 The longer patients went without progression, the more likely they had chemotherapy-sensitive disease.

[This regimen] is chemotherapy, so one is going to see adverse effects typical of chemotherapy, including anemia, neutropenia, thrombocytopenia, and fatigue.7 Most of these are grade 1 and 2, but then there is grade 3 fatigue. There was 2% grade 3 and 3% grade 4 febrile neutropenia. This is clearly [consistent with] chemotherapy. The ATLANTIS study had patients randomly assigned to a combination of lurbinectedin and doxorubicin vs topotecan or CAV. It was a negative study, and it is very difficult to know what to make of [those] data because [the study] used low-dose lurbinectedin at only 2 mg/m2.

Had they done their study with single-agent lurbinectedin, would that be a positive study? We don’t know that. That study is currently ongoing in other countries but not in the United States because in the United States, it’s approved. We’ll know the data in a few years.

### References


### Table. Efficacy Results of Phase 2 Study of Lurbinectedin for SCLC7•

<table>
<thead>
<tr>
<th></th>
<th>ALL PATIENTS (n = 105)</th>
<th>CTFI &lt; 90 DAYS (n = 45)</th>
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<td>Overall response rate</td>
<td>35.2%</td>
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<td>Disease control rate</td>
<td>68.6%</td>
<td>51.1%</td>
<td>81.7%</td>
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<tr>
<td>Median duration of response (months)</td>
<td>5.3</td>
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<td>Median PFS (months)</td>
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<tr>
<td>Median OS (months)</td>
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<tr>
<td>Deaths</td>
<td>63% (n = 66)</td>
<td>82% (n = 37)</td>
<td>48% (n = 29)</td>
</tr>
</tbody>
</table>

CTFI, chemotherapy-free interval; PFS, progression-free survival; OS, overall survival; SCLC, small cell lung cancer.

*Median 17.1 months of follow-up.

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**Case-Based Roundtable Meetings Spotlight**

**TUMOR TYPE**

**LUNG CANCER**


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**TUMOR TYPE**

August 2022  | Case-Based Roundtable Meetings Spotlight

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**LUKE:** This is an unresectable case, so let’s reflect on how we think about unresectable BCC. The NCCN guidelines considerations for BCC stratification [help] determine the options in terms of how to manage patients.1

The low- and high-risk categories can be dictated by factors such as the location and size, so truncal lesions that are small are lower risk. If the border is well defined, that’s a good thing, relatively speaking. If it’s a primary lesion, that’s better than a recurrent lesion. If it’s not associated with immunosuppression, prior radiation, or perineural involvement, those are all important features that predict better outcomes. The subtype, in terms of nodular or superficial, is in a lower-risk category.

Contrast that with the [high-risk group], where lesions on the extremities or on the trunk that are greater than 2 cm, or lesions located on the cheeks, forehead, scalp, neck, and tibia, or head, neck, hands—basically not the trunk—are higher risk. That often [speaks] to the ability to resect these lesions. If the borders are poorly defined, or it’s a recurrent lesion, that’s not good. If there’s associated immunosuppression, prior radiation, or perineural involvement, those are bad features as well. Then the subtype with an aggressive growth pattern is something that is not great, that we don’t want to see.

Dr Ferris, as you think about stratifying a case like this, are there any in particular of these factors that would sway you more than any others? I think our case is a little generic in this regard, but when you think about these things, which of these are the most impressive to you?

**FERRIS:** For this lesion, [I think about] the size and the location close to important anatomic structures—thinking about getting the appropriate margin on that, or clearing that, knowing that you’re right up against the nasal ala, and thinking about the closeness to the lower [eyelid] as well.

When we look at these, we’re thinking not just how do I get that tumor cleared, but how do I reconstruct that? Where am I going to get tissue, to...
bring that in? Those are all important features. And then the subtype, superficial basal cells, nodular basal cells tend to be a bit less aggressive and a little easier to clear. But some of those subtypes, like morpheaform or an atypical basal cell, can be harder to clear, too.

LUKE: Yes. When you think about the potential to do a Mohs procedure on the face vs a resection, which might take off part of the nose, how do you think about those kinds of considerations? What's the point where dermatologic management might need to transition to a full surgical approach?

FERRIS: I would definitely clear this with Mohs surgery. This is the classic case where the borders are poorly defined. You want to have complete margin assessment. I think, sometimes, Mohs surgery is seen as “less surgery,” but we think of it as surgery that lets you evaluate every single margin. If you just do a typical elliptical excision, and bread loaf through that tissue, the pathologist sees about 2% of the actual margin, so there are going to be big areas that aren’t evaluated. With Mohs, because of the way the tissue is processed, you can see the deep and peripheral margins. So for clearing it, [I would use] Mohs. If you’re going to plan to surgically clear, this is where multidisciplinary care comes in, with thinking about reconstruction. Oftentimes, these kinds of reconstructions can be done by most surgeons; however, if this was taking up half the scalp, you would want to think about a different closure reconstruction option.

- Given the high-risk features here, what are the treatment options?
- What are the overall unmet needs, clinically, in locally advanced and metastatic BCC?
- How do you view the pros and cons of each of the treatment options?
- Have you used Hedgehog pathway inhibitors [HHIs] in practice? If yes, what’s your experience?

LUKE: We talked about surgical approaches here and we’re describing this as unresectable, but we want to consider that in the context of a multidisciplinary team, because that determination is often quite complicated. Diagnosing someone as unresectable is a big deal because that sets them down a certain trajectory in terms of eventual outcome.

FERRIS: Patients with unresectable, locally advanced BCC oftentimes have other medical comorbidities. They might be significantly older. While sometimes very aggressive surgery might be an option for them if you only looked at the tumor, when you look at the patient, that patient may not be able to tolerate it. They may be on anticoagulants and have a lot of other issues that would make it hard.

In terms of unmet needs, we were excited when the HHIs came out because it was finally a systemic option for these patients. However, they’re not easy for all patients to tolerate. So I think an unmet need is having something for those patients who try an HHI and say, “I can’t tolerate this.”

When we have very young patients, we tend to think, Is this going to be a good option? What do we do here? This person is young; we’re committing them to long-term therapy with something that is going to have some adverse events [AEs].

EFIOM-EKAHA: I’ve used vismodegib [Erivedge] before, and it’s not the easiest thing to tolerate. The taste issues and all the other toxicities are pretty prominent and tough [Table]. My questions would be, for that patient for whom either the surgeon or the patient is [wary] of chopping off [the lesion]: What is the best option? How do we select it? Is there a preferred sequence, HHI vs PD-1–directed therapy? We all use immunotherapy in several tumor types and we’re [aware] of managing it but, again, drugs like this are not the easiest to tolerate.

LUKE: Absolutely. Anyone else have experience or want to give their opinion about how you might sequence things?

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**DISCUSSION QUESTIONS**
**BEED:** I’ve used an HHI in an older woman who came in and she had an unresectable tumor in the corner of her eye, in the inner canthus. She had put a Band-Aid over that, and she came in for something else. We treated her with [an HHI for the tumor] and she could tolerate it for maybe 6 months, then I’d take her off, put her back on, take her off. I have not changed it because it’s worked for her, and she’s now in her 90s. I would certainly use the other HHI as well. The other one is intravenous…and sometimes people can’t afford the [oral medication]. So that’s always a consideration, too.

**LUKE:** I think in clinical practice that relevance of intravenous vs oral is a big deal.

**MALHOTRA:** I had a patient at the VA [Veterans Health Administration] who I tried on cemiplimab [Libtayo] immunotherapy. There was a big lesion on his face, close to his eye, and he had stable disease for a long time.

**MISBAH:** I was almost able to use it, but I didn’t have the opportunity to use an HHI.

**AKBAR:** I have used an HHI in the past and the biggest trouble I had with that particular patient was bad muscle spasms, despite using the muscle relaxants. That was the reason we ended up discontinuing.

**LUKE:** You are raising important points on this. In terms of the pros and cons here—I think on a high level, is that the tolerability, generally speaking, of HHIs gets pretty tough after 3 months. I’m even surprised to hear that the 1 patient made it 6 months because most patients by about 3 months are having a tough time.

There are a lot of ongoing trials now, trying to look at pulsatile dosing, shortening the duration, taking breaks, and options like that. But it’s very interesting to think about when to use immunotherapy because if you determine that the patient would not tolerate an HHI, you can go to immunotherapy. The question is: When is that? Is that right away? Is that after you’ve tried it for a while? I think there is an intentional flexibility there that comes down to your clinical decision-making. But it is important to emphasize that Hedgehog inhibition can be quite powerful, in terms of controlling these lesions, and figuring out how to use it the best you can is an important consideration.

**CHOWDHARY:** I haven’t used vismodegib or sonidegib [Odomzo]. I see a lot of solid tumors, such as lung cancer; a lot of our patients with skin cancers go to the main campus. But I wanted to know, how do you differentiate between using one or the other? If I ever have a patient [in whom] I’m going to go for an HHI, how are you making the decision between vismodegib vs sonidegib?

**LUKE:** There are no head-to-head data so it’s going to be something about your familiarity, and probably your formulary considerations, in terms of which drug you can get more easily for a patient. I don’t think that there’s clear evidence that one is a lot better than the other. Whichever one you have familiarity with, or can get at a reasonable cost, is probably the way to go, in terms of choosing the in-class agents.

**CASE UPDATE**

The patient was started on vismodegib 150 mg by mouth daily.

**DISCUSSION QUESTION**

How long would you typically continue on a HHI?

**LUKE:** Dr Beed, you mentioned your patient with whom you did 6-month treatment intervals on that therapy, and that sounded like that was dictated by the tolerability. Would you have preferred to continuously dose, or do you think that that model of treatment breaks would be something that’s broadly applicable?

**BEED:** I think it worked well for her. She lost weight, didn’t have any sense of smell and taste, was weak, and had alopecia; we’d stop it and then she’d be all good. Then when it started growing, I’d start it [again]. This has happened about 4 or 5 times now. I’d certainly change her [treatment], but she’s much older, and I thought to put her on intravenous therapy would be a bit much. But she’s amenable to starting something. What do you do when this stops working?

**LUKE:** That’s the hard question. In the context of other tumor types, and with targeted therapy, my experience is that I often find a utility in treating until what appears to be best response, and then assessing tolerability at that moment. That can, for some patients, be a month of therapy, or 3 months; it depends. But I have a lower threshold for discontinuing if the patient is having a good treatment effect. Whereas, with some other targeted therapies, a resistance doesn’t arise quite so quickly to HHIs. It’s a therapy that we can commonly go back to. So I try not to drag the patient through the painful toxicity, and try to get to that response, and then try to take a break.

What is your experience in terms of intermittent dosing? Were you able to take breaks, or did you notice resistance?
EFIOM-EKAHA: My patient was metastatic so we kept going and, unfortunately, quality of life wasn’t that great.

FERRIS: When it was our only drug, taking breaks—people have studied different sequences of 8 weeks; go 6 months, 8 weeks on, 8 weeks off vs 8 weeks off, 12 weeks on. In reality, the protocols probably get tailored to what the patient is able to tolerate. I think that those breaks give patients the ability to stick with it a little bit longer.

As we have more options, I’m curious: Do you end up ever cycling back and forth—having somebody on an HHI, going to cemiplimab, and going back? Or would you see it as a break or a transition? “We’ve really maxed this out; now let’s move on to cemiplimab.”

LUKE: It all depends on the patient in front of us. I think that would be very reasonable. I haven’t personally done that yet, but I probably haven’t had the chance to. That emphasizes this question of when does intolerance come in? Because if you can transition over without having to document progression, this question of can you go back to it is a good one later on if you’re not getting the response.

I probably wouldn’t give anti–PD-1 more than once. But in terms of targeted therapy, I would definitely be willing to go back to the well multiple times. If there’s been a reasonable period of time, you can often get a second response. So I think that’s an important consideration also, that with these patients, owing to comorbidities and advanced age, we try to keep things on the rails over time. It’s not exactly the same thing as your 40-year-old patient who is looking for a “cure.”

FERRIS: There are some data for using L-carnitine supplementation for the myalgias. Do you ever end up trying that? There’s evidence for some of the things we use in dermatology for hair loss. It seems like, in general, what people don’t tolerate is the muscle cramping more than anything. Just curious if you feel like things like L-carnitine supplementation help or even get you that extra few months to see that response before you would want to transition them.

LUKE: Yes, it’s a good point. I haven’t seen it make a big difference, but I think it’s probably anecdotal experience. But what you raise is an important consideration, which is if you’re starting patients on HHI, get the patient set up with palliative care and with your nutritional support at your cancer center. That can go a long way toward allowing them to stay on drug for longer periods of time.

Some other factors we think of, as it’s targeted therapy, is it’s going to be well tolerated. This is not exactly that, and the more help you can get for the patient early on—especially if they’re someone who may not have the level of capacity that they might have had when they were younger.

Depending on their family involvement, these kinds of things can make a big difference in terms of maintaining area under the curve on exposure for patients. In other words, can they keep taking the drug? All of those are important considerations, emphasizing the multidisciplinary care of the patient.

DISCUSSION QUESTIONS
• In your experience, how long do toxicities persist after discontinuation of an HHI?
• How do you counsel the patients who are receiving this therapy?

LUKE: One other note that can help with some of these patients with the muscle pains is the use of amlodipine. How long did it take once you stopped the HHI to see some of the symptoms improve?

BEED: About a month to 6 weeks. She would say, “Christmas is coming; I want to feel good,” so we’d stop it. We’d do it around her holidays and vacations, what she felt was important.

LUKE: Yes, that’s an insightful comment. When we’re giving these palliative therapies—because in reality that’s what we’re talking about here—taking into account the patient’s real life, and what’s going to be meaningful to them, can be a very important thing.

My experience is similar. When patients get sick enough that they want to stop these drugs, it’s usually about 3 to 4 weeks that it takes before the symptoms start to get better. It’s probably going to be dependent, to some extent, on how robust your patient is in the first place. It sounds like your 90-year-old patient was quite the go-getter. It’s probably pretty variable, in terms of what their motivation is, in terms of trying to stay on the medicine. We emphasized [counseling the patients who are receiving HHIs]. Trying to get them set up with nutritional support and palliative care, to make sure that they’ll
get all the resources that they might be able to have, in order to help manage through the AEs that they are experiencing, is an important aspect to all of this.

The other thing that I’m going to note, in this context—the obvious outlier here is that many patients with BCC are going to be those associated with solid organ transplant or some other form of immunosuppression. In those scenarios, this question about immunotherapy becomes much more nuanced. There is no evidence from the clinical trial that you could give immunotherapy in that setting. In reality, there’s probably a reason they’re on immunosuppression.

So if you give them anti–PD-1 therapy, you’re probably running a pretty big risk that you’re going to do something bad. That’s another consideration here, and why it’s important to understand how to use HHIs, because anti–PD-1 therapy is not this panacea for all patients. Unfortunately, in skin cancer especially, you’re in a tough spot when thinking about that.

**DISCUSSION QUESTION**

What are some triggers to switch from an HHI? Or to refer to a medical oncologist?

**LUKE:** In our patient, what would we do next? What are the triggers for thinking about switching over from an HHI to anti–PD-1 therapy? We’ve alluded to a lot of them. Even those who haven’t used these drugs, how would you think about this?

**MISBAH:** I haven’t used an HHI but I’ve used PD-L1 therapy in other cancers and I would feel comfortable switching, or if it was referred from the dermatologist, to start them on a PD-L1 therapy, taking into consideration those things. You’re right; the patients who get BCC are on immunosuppressives in the first place. But in the case that they could be eligible for a PD-L1 therapy, I feel comfortable using them in other cancers. I haven’t used them often in BCC. I would be OK using it in BCC as well.

**LUKE:** Dr Malhotra, how would you think about this? The label is fairly vague; it says, “or intolerant,” so what constitutes intolerance? You have a lot of experience at the VA. The people at the VA often have a lot of comorbidities. He was cachectic, had lost a lot of weight, had significant bone pains and joint pains, and wasn’t ambulating well at home.

We did not wish to significantly affect his quality of life, and that was the way we decided we were going to stay away from the HHIs. But I think if patients are losing weight, and it has significantly affected quality of life, then that would be a trigger for me to switch at that time if I had started him on an HHI.

**BEED:** I’ve treated a patient with a PD-L1 inhibitor, too. We get surgeons who say, “We can’t do anything; take these patients.” It was fine; it worked well. Both of these [treatments] have worked great. [The lesion] was on his ear and the side of his face, but he was much older and had multiple comorbidities, and he went on to die of something else. I’ve used each of these a few times, and they seem to be very good.

I’m at a small hospital. We have 1 palliative care [unit], which is more like a hospice. So we have to do all this, and spend the time—my nurse practitioner and I—to get them through these AEs, go over everything, and get to know them. It’s a small town, so if I don’t know them, somebody knows them, or their grandmother knows them. You get to give very personalized medicine that way.

**LUKE:** I’m also quite comfortable giving anti–PD-1 therapy in the context of other cutaneous malignancies. I would be thinking about it from the perspective of disease control. If it’s a lesion that isn’t otherwise out of control, I might be leaning toward anti–PD-1 relatively earlier than later, because if it’s not urgent, you might get 1 of those patients who can go a very long time benefiting from that. However, if their lesion’s quite gnarly [in terms of] putting the anatomic structures in place, I’m probably going to try to treat at least until maximum treatment response, if the patient can tolerate that, and go as long as we can before we think about switching over.

**REFERENCES**

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 × 10⁹/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 intermittent 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.
COMFORT-I Primary Endpoint: of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24 vs 0.7% of patients receiving placebo (P < 0.0001).

COMFORT-I Secondary Endpoint: of patients receiving Jakafi achieved a ≥50% improvement in Total Symptom Score (TSS) at week 24 vs 5% of patients receiving placebo (P < 0.0001).

COMFORT-I 5-year analysis: Jakafi and placebo

Overall Survival Kaplan-Meier Curves by Treatment Group in COMFORT-I

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</tr>
<tr>
<td>2</td>
<td>0.63</td>
<td>0.74</td>
</tr>
<tr>
<td>3</td>
<td>0.47</td>
<td>0.56</td>
</tr>
<tr>
<td>4</td>
<td>0.31</td>
<td>0.42</td>
</tr>
<tr>
<td>5</td>
<td>0.16</td>
<td>0.26</td>
</tr>
</tbody>
</table>

At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo.

Overall survival was a prespecified secondary endpoint in COMFORT-I.

 Jakafi 5-year overall survival probability was 53%.

All patients in the placebo group either crossed over to Jakafi at a median of 9 months or discontinued.

Interwne with Jakafi at diagnosis in appropriate patients with MF

STARTWITHJAKAFI.COM

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

**INDICATIONS AND USAGE**

Myelofibrosis: 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. Polycythemia Vera Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea. Acute Graft- Versus-Host Disease Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGvHD) in adult and pediatric patients 12 years and older. Chronic Graft- Versus-Host Disease Jakafi is indicated for treatment of chronic graft-versus-host disease (cGvHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Adverse Reactions (6.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2) in Full Prescribing Information]. Delay starting therapy with 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**

Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. In initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination.

**Progressive Multifocal Leuкоencephalopathy**

Progressive multifocal leuкоencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. Hepatitis B Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

**Symptoms Following Interruption or Discontinuation of Treatment with Jakafi**

Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory symptoms, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any current illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue therapy with Jakafi without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [see Dosage and Administration (2) in Full Prescribing Information], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.

**Non-Melanoma Skin Cancer**

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Monitor and treat according to clinical guidelines for the management of hyperpigmentation.

**Major Adverse Cardiovascular Events**

Another JAK-inhibitor has increased the risk of cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors.

Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Thrombosis Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors.

Patients who are current or past smokers should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Thrombosis Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors.

**Secondary Malignancies**

Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSCR (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients with a malignancy (other than a successfully treated NMSCR), patients who develop a malignancy, and patients who are current or past smokers. ADVERSE REACTIONS The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: Thrombocytopenia, Anemia and Neutropenia [see Warnings and Precautions (5.1) in Full Prescribing Information]. Myelofibrosis The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy in a double-blind randomized placebo-controlled study ofJakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologice adverse reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received 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 Reactions</th>
<th>Jakafi (N=195)</th>
<th>Placebo (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Bruising</td>
<td>31</td>
<td>20</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>
of treatment because of thrombocytopenia occurred in
< 1% of patients receiving Jakafi and ~ 7% of patients
receiving control regimens. Patients with a platelet count
of 100 x 10^3/L to 200 x 10^3/L before starting Jakafi had
a higher frequency of Grade 3 or 4 thrombocytopenia
compared to patients with a platelet count greater than
200 x 10^3/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 hematologic 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=150)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70 9 1 7 0 1 0 1 0</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>96 34 11 87 16 3 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 5 2 4 1 1 1 0 0</td>
<td></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 patients treated with Jakafi and
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 patients with Jakafi and 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-controlled 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 nonhematologic 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=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades 3</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 0 &lt; 1 3 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 0 1 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Dryness</td>
<td>13 3 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 3 1 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>6 &lt; 1 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>6 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>8 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 &lt; 1 &lt; 1 &lt; 1 &lt; 1 &lt; 1 &lt; 1 &lt; 1</td>
<td></td>
</tr>
</tbody>
</table>

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

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>All Grades 3</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>77 &lt; 1 &lt; 1 &lt; 1 58 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 5 0 24 3 &lt; 1 &lt; 1 0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 0 &lt; 1 10 &lt; 1 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35 0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25 &lt; 1 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>23 0 0 23 0 0 0 0 0</td>
<td></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 cGVHD failing treatment
with steroids with or without other immunosuppressive drugs [see Clinical Studies (14.4) in full Prescribing Information].
The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to
Jakafi. 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
anemia and thrombocytopenia. The most common
nonhematologic adverse reactions (incidence > 20%) are
infections (pathogen not specified) and viral infection. Table 7
presents the most frequent nonlaboratory 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%) Nonlaboratory
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=116)</th>
<th>Best Available Therapy (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades 3</td>
<td>Grade ≥ 3</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>45 15 44 16</td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>28 5 23 5</td>
<td></td>
</tr>
</tbody>
</table>

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 Test</th>
<th>Jakafi (N=116)</th>
<th>Best Available Therapy (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades 3</td>
<td>Grade ≥ 3</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>82 13 75 8</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 12 23 9</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 20 54 17</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28 10 85 8</td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>65 5 54 6</td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>73 11 71 16</td>
<td></td>
</tr>
<tr>
<td>Gamma glutamyltransferase</td>
<td>31 42 75 38</td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>47 40 2</td>
<td></td>
</tr>
<tr>
<td>Elevated lipase</td>
<td>38 12 30 9</td>
<td></td>
</tr>
<tr>
<td>Elevated amylase</td>
<td>35 8 25 4</td>
<td></td>
</tr>
</tbody>
</table>

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

Clinically relevant laboratory abnormalities are shown in Table 4.
The safety and effectiveness of Jakafi 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 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. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to < 17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m² twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (61%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with longer-term treatment is unknown. Adverse events 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 Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with aGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Renal Impairment Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment, and ESRD (CLcr less than 15 mL/min) on dialysis [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Modify Jakafi dosage as recommended [see Dosage and Administration (2.6) and Clinical Pharmacology (12.3) in Full Prescribing Information]. Hepatic Impairment Exposure of ruxolitinib increased 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].
Roundtable Discussion: Bryce and Colleagues Consider Treatment Options in Metastatic Castration-Sensitive Prostate Cancer

CASE SUMMARY

A 73-year-old man presented with urinary retention, fatigue, and decreased appetite. He had no family history of prostate cancer and is active, but biopsy revealed adenocarcinoma of the prostate gland with a Gleason score of 8 (4 + 4) and disease in 10 of 12 cores. His prostate-specific antigen (PSA) level was 150 ng/mL, his hemoglobin (Hb) level was 9.7 g/dL, and his absolute neutrophil count (ANC) was 1.9 × 10⁹/L; his liver function tests were abnormal. He received a diagnosis of localized high-grade prostate cancer in September 2018 and underwent robotic radical prostatectomy with a subsequent PSA decrease of 0.2 mg/mL. CT and bone scans showed no residual disease.

However, the patient eventually complained of right hip pain and abdominal pain, and further imaging with CT and bone scans showed multiple metastatic bone lesions in his pelvis and diffuse liver lesions. His new PSA level was 90 ng/mL, his Hb level was 9.4 g/dL, and his ANC was 1.5 × 10⁹/L. He then received a diagnosis of metastatic prostate cancer, but his germline genetic testing was negative. He wishes to receive oral treatment and avoid chemotherapy and minimizing adverse events (AEs) is important to him.

DISCUSSION QUESTIONS

• Which therapeutic options would you consider for this patient with high-volume, hormone-naïve metastatic prostate cancer?
• How do you decide between the treatment options?
• What factors most influence your treatment selection?

HERMEL: It’s obviously based on patient preference. If they have high-burden disease, then you’re basically going to try to get something that would reduce the burden quickly.

That would be, ideally, something like chemotherapy with docetaxel [Taxotere]. The use of other therapies, such as abiraterone [Zytiga] and enzalutamide [Xtandi], would then be based on the AE profile and patient preference.

BRYCE: Is there a particular set of toxicity data that drives you when you think about the comparison of these drugs?

HERMEL: Yes, the patient’s baseline liver function for abiraterone.

STEPHEN: I am most comfortable using doublet therapies. I haven’t tried to use triplet therapies before, but for a lot of the patients I see I wonder if they could handle the toxicity of a triplet therapy. However, I do agree that you’d have to take into account the burden of disease, the pace of disease. I rarely use abiraterone now, as I’m very comfortable using enzalutamide. I am hoping to learn more about how to use molecular test results, because I’m not sure about that.
**DISCUSSION QUESTIONS**

- During clinical decision-making, how and when do you consider patient-reported outcome data, patient preference, and patient goals of therapy?
- How do you balance therapeutic intensity and quality of life?
- How do you counsel this type of patient about next steps and options at this point?
- What is your experience with patients’ perceptions and preferences about their options?

**BANSAL:** There’s no perfect answer; it just depends on patient age, patient preference, comorbidities, and tumor burden. I have patients who are 90 years old with de novo metastatic disease and other patients who are 56 years old. So it depends on, mostly, their comorbidities, age, and the treatment goals.

**GOLDFARB:** Most patients don’t want chemotherapy when you bring it up, so you must discuss that with them. My options for this patient would be chemotherapy, and anti-androgen therapy, but I would certainly want to discuss chemotherapy. After that, you’ve got to start thinking about PD-L1 or PARP inhibitors if the patient is BRCA positive.

**YOO:** I think the patients don’t like the word chemotherapy. There’s a benefit to using aggressive chemotherapy, so I try to convince them [to use it]. If the patient is concerned about toxicity, then I can always start on the lower dose, but I try to do chemotherapy if the patient has visceral disease. If not, I don’t think there is a wrong treatment.

**SARACENI:** For this patient I would be worried because there was possibly some impending liver failure, with bulky disease in the liver. With a younger, fit patient I would try to push toward chemotherapy; but, like most of us said, if patients have any other option but chemotherapy, they’ll do it. So I take patient preference and what they want to do highly into account when I counsel them.

**GONZALES VELEZ:** A perception that I see is that patients think that chemotherapy is like a taboo or a stigma word, and they think that targeted therapy, especially oral therapies, don’t have AEs. Sure, they are different from chemotherapy, but they can also have AEs. So I think it’s important to explain to patients that targeted therapies or hormonal therapies also have AEs, different from chemotherapy but they also have their issues.
BRYCE: Yes, absolutely. People come in with preconceptions: Why is 5-FU [fluorouracil; Adrucil] scary but capecitabine [Xeloda] isn’t? It’s the same drug, but there is that oral-intravenous [IV] divide. There’s also the semantics of what is chemotherapy vs what is a targeted therapy. So absolutely, there’s a lot of power in words, and I think we see that in the clinic every day.

DISCUSSION QUESTIONS

• What is your reaction to the updated results from the TITAN study (NCT02489318) of apalutamide (Erleada) and ADT?¹
• What is your reaction to the final overall survival (OS) from the ARCHES study (NCT02677896) of enzalutamide and ADT?²
• What toxicities are most concerning to you in this setting? Which do you find most challenging to manage?

MAR: I think that all oral therapies are equivalent per the data that’s been reported in large, randomized phase 3 trials. So there are no preferred agents in terms of effectiveness [From The Data³]. I typically pick based on toxicity and insurance reimbursements.

But there was 1 small study that looked at sequencing of therapies in the castrate-resistant setting.⁴ And just knowing about AR-V7 mutations, [findings from] that showed that giving abiraterone before enzalutamide may lead to a slight chance of response to enzalutamide down the road, as a second therapy, and vice versa. I think the chance of response was 0% in that small study, so it was a little different in terms of setting because this is hormone-sensitive disease. I do gravitate toward abiraterone or apalutamide most of the time, less so with enzalutamide. More recently I’ve been using triplet therapies rather than doublet therapies. So not so much apalutamide single agent anymore.

HSU: Yes, I agree, most of us are comfortable using both. I’ve been using a little bit more of enzalutamide plus ADT lately, but I think the cost is the issue. I think they’re not that different in terms of efficacy, from the [data from the] 2 studies, the TITAN and the ARCHES studies.

SUD: I have used enzalutamide much more [often] than apalutamide in my own practice, [so have more] familiarity with that. I am familiar with these data and I find that [the enzalutamide] is well tolerated. Fatigue is a big AE that many patients do complain about. Of course, we also must watch their liver function tests [LFTs] but otherwise, they are fairly well tolerated.

SPILLANE: I tend to use apalutamide. I think it’s a well-tolerated drug. With enzalutamide, early on when they were first talking about it, I did have a few patients who had falls, elderly patients. And then it became clear that there is some central nervous system penetration, and it’s not exactly clear why, but you have some older gentlemen who will either get dizzy or have a fall, or something like that. When I’ve run into that, I’ve ended up having to reduce the doses. You do see that also with apalutamide but probably less so with darolutamide [Nubeqa]. I’ve [become] comfortable using apalutamide and potentially adjusting doses in those older patients who get the dizziness, and even in those patients [in whom] you’re worried about high risk of fall.

STEPHEN: With apalutamide, you—as opposed to chemotherapy—watch the LFTs, probably with monthly labs, to

FROM THE DATA

When comparing the ARCHES (NCT02677896) and TITAN (NCT02489318) trials, investigators did not see a strong advantage between enzalutamide (Xtandi) or apalutamide (Erleada).³ In ARCHES, at a median follow-up of 44.6 months, median overall survival (OS) was not reached but there was a significant improvement of OS in the enzalutamide group (HR, 0.66; 95% CI, 0.53-0.81; \(P<.001\)). OS at 24, 36, and 48 months in the treatment arm vs placebo arm was 86% vs 82%, 78% vs 69%, and 71% vs 57%, respectively. In comparison, at a median follow-up of 44 months, the TITAN trial also did not reach median OS, but apalutamide significantly reduced the risk of death by 35% (HR, 0.65; 95% CI, 0.53-0.79; \(P<.0001\)) and when adjusting for crossover, the risk of death went down by 48% (HR, 0.52; 95% CI, 0.42-0.64; \(P<.0001\)).
make sure they’re not having worsening castration-related symptoms, as opposed to [when they’re on] docetaxel. I personally have had bad experiences when adding docetaxel on. It’s a lot of lower-extremity edema, especially with situations where you have to use prednisone. What I usually use is enzalutamide as opposed to apalutamide, and in men who are over 80 I haven’t had the fall issue, [as mentioned earlier].

**BRYCE:** What about imaging? What do you do for imaging in these patients? [How do imaging and other findings trigger you to consider changing therapies?]

**STEPHEN:** This person’s advanced in this case, so every 2 months you might get CAT scans and a bone scan, or a PET scan. It depends on the pace of the disease, however, I have a hard time adding docetaxel on to these regimens. I’ve had a few cases where they are already too symptomatic from the prostate cancer by the time they presented. If you’re adding docetaxel, you must follow them much more closely.

**SURESH-CHANDAR:** You are going to be monitoring the PSA [level] closely, and if you’re seeing a rising PSA, or onset of any new symptoms, then that could potentially prompt you to get imaging to get a better understanding of the disease status. But a combination of those things usually triggers me to consider changing or adding therapy.

**DISCUSSION QUESTIONS**

- How do you counsel and educate your patients receiving combination therapy for these various regimens?
- How do you ensure that your patients are able to complete therapy?
- When patients are receiving oral therapy, are you satisfied that they are adhering, or how do you monitor that?

**VELEZ:** We have discussed the importance of the timing of the oral medications vs chemotherapy. You tell them about the toxicity, the steroid component, the fall risk with the enzalutamide, and the hypertension. You tell them the red flags and the risk factors that they should be on the lookout for and to call the office if anything happens.

I pretty much trust the patients that they’re able [to adhere], but I let them know they can skip 1 dose here and there, to give them a little bit of flexibility. I trust most of the patients when they tell me that they stopped the medication or they skipped a few doses. I think with a good physician and patient relationship, most of the patients are honest when they skip or if they stop the medication for any reason.

Now, what percentage of patients who are referred to you have already begun ADT monotherapy for their metastatic castration-sensitive prostate cancer [mCSPC]? We’ve got a variety. When it comes to GU [genitourinary] practices, and the relationship with the urologists and the radiation oncologists, I always say if you’ve seen 1 practice, you’ve seen just 1 practice, because every situation is different. I guess anybody who has most of their patients coming in already on ADT [would ask], what’s the nature of your treatment pattern? Who’s starting these patients on ADT? Just make it an open question [as you discuss next steps for treatment].

**GOLDFARB:** In my practice, the ones I see from urologists all the time are on ADT. I’ve never seen them not getting leuprolide [Lupron] when they’re from the urologist.

**BRYCE:** Do the urologists then ship them right away because they’re metastatic, or is that something that happens later?

**GOLDFARB:** In my practice, it’s after they relapse or treatment is no longer working, and then I see them. I never see them up front from the urologists.

- What role (if any) do you see for triplet therapy in this setting? Are you or any of your colleagues currently using it?
- What data have influenced and/or changed your practice with respect to mCSPC?

**SARACENI:** I personally have not used triplet therapy in my practice yet.

**BRYCE:** If I saw a patient like this in my practice, I would be thinking to myself, “Triplet is what I ought to do,” and then I would have to convince myself why I wouldn’t. It might be because of patient preference, of course; might be liver function, etc, but it’s always on my mind.

You want to get that fast response when you have these aggressive diseases. Apalutamide and enzalutamide are great drugs, there’s no question. They’re effective, they’re well established. Reflecting on some of the comments earlier, I don’t feel like there’s a lot of daylight between the 3 oral options in terms of their overall efficacy. Choosing between the oral agents is largely a question of toxicities, tolerance, and then insurance coverage. Every now and then, you get some insurance company that prefers one over the other.
**MAR:** I’ve been using abiraterone/docetaxel based on the PEACE-1 data [NCT01957436], but I do think darolutamide is probably a little more tolerable from previous experience. So I would like to use darolutamide now if insurance will allow me, but I think that triplets are coming, and that’s the future for this space.

**BRYCE:** Yes. They managed to do ABVD [doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine] for patients with breast cancer in the ’70s, and we’re still tiptoeing toward combination therapy in prostate cancer. They did that before there were antiemetics.

**MAR:** I also think it’s interesting that patients accept chemotherapy just fine if they have breast cancer, colon cancer, or pancreatic cancer. So why is prostate cancer so different, because breast cancer is also hormonal driven and patients accept chemotherapy just fine?

I think maybe that’s a way to think about it, we just have to educate the patients that if you get such an improvement in efficacy metrics, then why are we not giving chemotherapies in mCSPC together with the second-generation hormonal drugs?

**BANSAL:** If you have a younger patient who’s on docetaxel in the front line for de novo metastatic disease and is doing well, would you add darolutamide before the sixth cycle so that you could keep him on it, rather than just ADT after 6 cycles?

**BRYCE:** So far, the darolutamide label hasn’t been expanded, so I’m not sure I could get it approved. I’m hoping we’ll see a label expansion and we can get it in the metastatic castration-sensitive space, because right now it’s approved for nonmetastatic castration-resistant prostate cancer. I think it was a good study, with clean data; I expect there’s going to be a label expansion and National Comprehensive Cancer Network (NCCN) recommendations. So I think in the future I’ll be comfortable adding darolutamide in that space.

But as of today, I’m doing docetaxel followed by abiraterone, because that’s the PEACE-1 data and you can get it approved. We’re doing docetaxel in about 20% of the patients overall, and doublet in about 80%. That practice is driven in a large extent by thinking about risk. Obviously, if we think someone’s headed toward neuroendocrine disease, then we’re jumping in with chemotherapy much earlier and also looking at the genomics. That’s not standard of care, that’s not in the NCCN guidelines, that’s just the result of having looked at several hundred of these reports in castration-sensitive disease.

**REFERENCES**
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-SCLC.3*†

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.

Indication
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).

Select Safety Information
There are no contraindications for IMFINZI® (durvalumab).

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 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**

![Graph showing overall survival benefit at 3 years with IMFINZI + EP vs EP alone.](image)

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Probability of overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>52.8%</td>
</tr>
<tr>
<td>24 months</td>
<td>43.3%</td>
</tr>
<tr>
<td>36 months</td>
<td>22.9%</td>
</tr>
</tbody>
</table>

**Number of patients at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMFINZI + EP (n=268)</td>
<td>268</td>
<td></td>
</tr>
<tr>
<td>EP (n=269)</td>
<td>269</td>
<td></td>
</tr>
</tbody>
</table>

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

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**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%).
- 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).

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**NEW CASPIAN 3-YEAR OVERALL SURVIVAL ANALYSIS**

**IMFINZI + EP** vs **EP**

**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)
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% (37/1889) 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. Hyperthyroidism can follow hypothyroidism. 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 corticosteroids can be used. Immune-mediated 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/PD-L1 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 intervention 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 nausea (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


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IMFINZI®

Injection for Intravenous Use 50 mg/mL

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**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.

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 Patients with a body weight of 30 kg or more: 1500 mg in combination with chemotherapy every 21 days (week 1/2) for 4 cycles, followed by 1500 mg every 4 weeks as a single agent</td>
<td>Until disease progression or unacceptable toxicity</td>
<td></td>
</tr>
<tr>
<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>
<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.

**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 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>Pneumonitis</td>
<td>Grade 2</td>
<td>Withhold*</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Withhold*</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Grade 3</td>
<td>Withhold*</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis with no tumor involvement of the liver</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 tumor involvement of the liver*</td>
<td>ALT or AST increases to more than 8 times ULN or total bilirubin increases to more than 3 times the ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Grade 3</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>Grade 4 increased blood creatinine</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Exfoliative Dermatologic Conditions</td>
<td>Suspected SJS, TEN, or DRESS</td>
<td>Withhold*</td>
</tr>
<tr>
<td>Confirmed SJS, TEN, or DRESS</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Grade 2, 3, or 4</td>
<td>Withhold*</td>
</tr>
<tr>
<td>Neurological Toxicities</td>
<td>Grade 2</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
</tbody>
</table>

*Admit positive for infection before IMFINZI administration. Withhold IMFINZI if infection is not resolved or worsens during treatment. If infection does not respond to treatment or if infection persists, discontinue IMFINZI

**Preparation and Administration**

**Preparation**

- **Usual:** 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)
  - 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-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 1 (PD-1) or the programmed death ligand 1 (PD-L1) receptors.

Dose-dependent immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, exfoliative dermatologic conditions, myositis, and myocarditis. These reactions may occur as a result of redistribution or accumulation of antibody within specific tissues or organ systems.

Immune-mediated adverse reactions can occur at any time during treatment with PD-1/PD-L1 blocking antibodies and can present with or without prior evidence of inflammatory disease.

**Immune-Mediated Colitis**

Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) of IMFINZI in combination with chemotherapy. Most patients were successfully treated with corticosteroids.

**Immune-Mediated Hepatitis**

Immune-mediated hepatitis with no tumor involvement of the liver occurred in 0.1% (2/1889) of patients receiving IMFINZI, including Grade 4 (<0.01%) of IMFINZI in combination with chemotherapy. Most patients were successfully treated with corticosteroids.

**Immune-Mediated Hepatitis with Tumor Involvement of the Liver**

Immune-mediated hepatitis with tumor involvement of the liver occurred in 0.1% (2/1889) of patients receiving IMFINZI, including Grade 4 (<0.01%) of IMFINZI in combination with chemotherapy. Most patients were successfully treated with corticosteroids.

**Immune-Mediated Endocrinopathies**

IMFINZI can cause immunemediated endocrinopathies. The incidence of endocrinopathies 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% (54/1414), 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 therapy within 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (33/179) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475), 11.1% 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 infliximab with high-dose steroids.

**Immune-Mediated Adverse Reactions**

**Immunemediated Colitis**

IMFINZI can cause immunemediated 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.

**Immunemediated colitis occurred in 2% (37/1888) of patients receiving IMFINZI, including Grade 4 (0.1%) and Grade 3 (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 immunemediated colitis, while 2 patients (2/37) required other immunosuppressants (e.g. infliximab, mycophenolate).**
Immunemediated 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 (0.5%) required use of mycophenolate with high-dose steroids.

Immunemediated Endocrinopathies

Adrenal Insufficiency: IMFINZI may 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].

Immunemediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including 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 hypothryoidism. Initiate symptomatic treatment including hormone replacement as clinically indicated. Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2) in the full Prescribing Information].

Grade 3 hypophysitis/hypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI. Treatment with systemic 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 institute 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: Immunemediated 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 immunemediated hypothyroidism, while 6 patients (9/39) required endocrine therapy.

Hypothyroidism: Immunemediated hypothyroidism 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 (3/39) with immunemediated hypothyroidism, while 30 patients (30/39) required endocrine therapy.

Immune-mediated hypothyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI. 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: IMFINZI 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].

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 (0.1%, 2/1889) 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 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), has occurred with PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate for treatment of non-exfoliative rashes. Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2) in the full Prescribing Information].

Immunemediated rash or dermatitis occurred in 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.1%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immunemediated dermatology reactions.

Other Immunemediated Adverse Reactions:

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

Cardio Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including status asthmaticus). Muscle weakness in relation to an immune-mediated mononeuropathy/mononeuropathy gigantocellularis (with autonomic involvement). 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 immunemediated 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, arthropathy, polymyalgia rheumatica.
disruption of PD-L1 signaling was shown to result in an increase in fetal loss. The effects of durvalumab by maintaining maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, clinically recognized pregnancies is 2-4% and 15-20%, respectively. 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.

Table 6. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the CASPIAN study

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>IMFINZI with Etoposide or Carboplatin or Carboplatin N = 266</th>
<th>IMFINZI with Etoposide or Carboplatin or Carboplatin N = 266</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Grade ≥ 3 or 4 (%)</td>
<td>Grade ≥ 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>3.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1.5</td>
<td>3.1</td>
</tr>
<tr>
<td>TSH decreased &lt; LLN4 and ≤ LLN at baseline</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

1 The frequency cut-off is based on any grade change from baseline
2 Grade ≥ 3 or 4 (%)3 Grade ≥ 3 or 4 (%)4

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.

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.

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

Immun-Mediated 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.
- Coils: 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 aspecitic meningitis, immune thrombocytopenia, myocarditis, hemolytic anemia, myositis, uveitis, keratitis, and myasthenia gravis.

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or 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).

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
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**Hutson Walks Through Updates in the Management of Clear Cell RCC**

**CASE**

- A 59-year-old Black woman who received a diagnosis of clear cell renal cell carcinoma (RCC) underwent left radical nephrectomy in December 2019.
- Nine months later, she developed metastatic disease in both lungs, mediastinum (35 × 38 mm), and retroperitoneal lymph nodes.
- Diagnosis: stage IV RCC, clear cell histology with metastases to lungs and retroperitoneum
- Karnofsky performance status: 90%
- Hemoglobin: 11.1 g/dL
- Corrected calcium, neutrophils, platelets: within normal limits

**POLLING QUESTION**

At a live virtual event, Hutson asked participants, “What frontline therapy are you most likely to choose for this patient?”

- Axitinib + pembrolizumab 50% (5)
- Lenvatinib + pembrolizumab 30% (3)
- Nivolumab + ipilimumab 20% (2)
- Cabozantinib + nivolumab 0% (0)
- Cabozantinib 0% (0)
- Other 0% (0)

Total votes: 10

**Targeted Oncology™: What frontline therapy are you most likely to choose for this patient?**

**HUTSON:** The April 2022 National Comprehensive Cancer Network (NCCN) treatment guidelines have recommendations for poor- or intermediate-risk patients with clear cell RCC. There is no wrong answer here [because] everything is category 1, outside of single-agent cabozantinib [Cabometyx], which was approved based upon a phase 2 trial in the intermediate- or poor-risk population—and that is likely why it does not have a category 1 recommendation, as it was not a phase 3 study.¹ But the FDA has approved it [because] it showed superiority for first-line therapy in patients who are immuno-oncology [IO] intolerant or have a contraindication for IO use.² Cabozantinib would be certainly high on the list of agents one would choose from.

**What data support the recommended frontline regimens for poor- or intermediate-risk patients with clear cell RCC?**

The first-line immune checkpoint inhibitor combination trials have updated efficacy data. There’s IO dual combination from the CheckMate 214 study [NCT02231749], which is somewhat unique because it is 2 immunotherapies. The other 3 trials are IO/tyrosine kinase inhibitor [TKI] combinations. So comparing them head-to-head, an IO plus TKI to an IO plus IO is somewhat like comparing apples to oranges a little bit, but that’s what we’ve got to do. Among the IO-plus-TKI trials, cross-trial comparisons would be the most reasonable, and lenvatinib [Lenvima] plus pembrolizumab [Keytruda] is the most recently FDA approved combination.³ The problem is that all 4 trials have different lengths of follow-up, so we have data points that are at various levels of maturity. This has factored into reasons why some physicians may choose one therapy over the other.

The CheckMate 214 [data of] ipilimumab [Yervoy] plus nivolumab [Opdivo] are the most mature, and they’ve published the 5-year outcome data, where patients have maintained durability of benefit 5 years out. Some patients were able to get off therapy, so there’s excitement [about this regimen]. The median overall survival [OS] from the intention-to-treat analysis was 55.7 months vs 38.4 months for the comparator arm [HR, 0.72; 95% CI, 0.62-0.85].⁴ The HRs for all 4 trials were virtually within the same range, so you can’t separate them out based on HR, except the fact that you have a longer follow-up. The HR for CheckMate 214 is much more mature, and it’s double what’s been reported for the...
clearance study [NCT02811861] and CheckMate 9ER study [NCT03141177]. So will these IO-plus-TKI combinations maintain their HR with a longer follow-up? That is the concern, but across the board, the benefit seems to be similar based on the HR.

The landmark OS [rates] at 12 months and 24 months—and one could say those are very early landmarks—show how things separate out, so it’s hard to show a lot of benefit. The OS [rates] after 24 months all range from 71% to 79%, and the progression-free survival [PFS] rates show differences in HRs for the 4 trials. Whether the length of follow-up is influencing the HR is certainly a point that could be made, and I would argue that it does. You generally lose the HR in PFS over time, as people progress. For instance, CheckMate 214 has a PFS HR of 0.86, which is the worst of the HRs, whereas the CLEAR study has the shortest follow-up and newest agent [has] a very attractive HR of 0.39. For the overall response rates [ORRs], something that’s striking is the CheckMate 214 response rate, which is certainly less—and maybe almost in some situations 40% to 50% less—than what you’re seeing with an IO plus TKI. The complete response [CR] rates look similar with the CLEAR study having the highest CR rate of 16%. In terms of the progressive disease [PD] rates, the CheckMate 214 [trial] has much higher PD rates than what you see with the other agents.1-7

**How would you interpret these data?**

It’s difficult to look at this type of data and try to be fair and unbiased...because you’re looking at data...at various levels of maturity. I think what would be fair to say is the dual IO regimen has this long-term follow-up data in which there is a group of patients [appearing] to have durable responses. [About] 20% to 30% of patients who are still on therapy...have had near-CRs or partial responses [PRs] that have been durable, as well as 10% to 12% of people with CRs who may be off therapy.

In about 30% to 40%, or one-third, of patients, the dual IO does not work at all.8 So after the first scan is done, there’s progression. We have a longer follow-up and durability, but it’s not as generalizable; it doesn’t work in as many people. The IO-plus-TKI regimens, on the other hand, work in more people, so you have clinical benefit rates in the 90% range: 90% to 95% with the CLEAR study, about 90% with CheckMate 9ER, and for the KEYNOTE-426 trial [NCT02853331], a roughly 85% clinical benefit rate, which is stable disease, CR, and PR.

They’re going to work in more people, but we don’t have that long-term follow-up to know over time if we are able to maintain responses. Is there going to be any type of flattening of a curve that would suggest that there is a cure possibly? We don’t know that yet with these 3 studies because we just don’t have mature data out yet, so that’s about as fair and unbiased as we can get.

**CASE UPDATE**

The patient received pembrolizumab plus lenvatinib as part of a clinical trial.

**What data support the use of lenvatinib plus pembrolizumab as frontline therapy in advanced clear cell RCC?**

The phase 3 CLEAR study had lenvatinib plus pembrolizumab vs everolimus [Afinitor] vs sunitinib [Sutent]. US Oncology Research and Texas Oncology participated in this trial, and one of the authors of the trial was on the steering committee.

The trial was a large international effort, [randomly assigning] patients with advanced clear cell RCC, measurable disease, and good organ function to receive either lenvatinib plus pembrolizumab, at a 20-mg lenvatinib starting dose plus pembrolizumab 200 mg every 3 weeks, with 50 mg of sunitinib given orally on a 4-weeks-on-and-2-weeks-off schedule; or lenvatinib plus everolimus, [at 18 mg of lenvatinib and 5 mg of everolimus]. It was a 1:1:1 3-arm trial, and...the power and statistics were done so that each of the lenvatinib-containing arms were compared with sunitinib—so the lenvatinib arms weren’t compared [with each other].7 Our focus is on the lenvatinib plus pembrolizumab arm vs the sunitinib arm, although lenvatinib plus everolimus fared well against sunitinib, but it is not relevant for us in the frontline setting.

The primary end point of the study was PFS, and secondary end points included OS, ORR, safety, and health-related quality of life. Some exploratory end points were duration of response and identifying biomarkers. There was prespecified stratification [of patients on the trial] into favorable-, intermediate-, or poor-risk categories, as well as geographic region.

The primary end point of PFS at a median follow-up of 26.6 months was 23.9 months for lenvatinib plus pembrolizumab vs 9.2 months for sunitinib [HR, 0.39; 95% CI, 0.32-0.49; P < .001], with the difference at 14.7 months.7 This is the greatest PFS that we’ve ever seen of a therapy in the frontline setting in kidney cancer. The PFS results favored the 2 combination regimens over sunitinib across all the evaluation end points, including Memorial Sloan Kettering Cancer Center [MSKCC] or the International [Metastatic RCC] Database Consortium [IMDC] risk groups.
How does the subgroup analysis impact the implications of these data?

The subgroup analysis by blinded review had several baseline demographics that showed if any prespecified stratification criteria, including adverse prognostic features, benefited lenvatinib plus pembrolizumab or not. Across the board, everything benefited lenvatinib plus pembrolizumab; irrespective of age, sex, and geographic region, lenvatinib plus pembrolizumab was superior.7

What’s great for us as oncologists, irrespective of the IMDC or MSKCC risk group, you don’t have to calculate their risk scores. This drug will work across the board in all the risk groups. You don’t need to worry. Subgroups based on performance status, PD-L1 expression, sites of metastases, prior nephrectomy, sarcomatoid histology, liver metastases, and bone metastases all benefited equally with the lenvatinib plus pembrolizumab.

The OS at median follow-up of 26.6 months showed a separation of curves in favor of lenvatinib plus pembrolizumab over sunitinib. There is crossing later, but that’s a small number of events that are not statistically valid. The HR is very attractive at 0.66 in favor of lenvatinib plus pembrolizumab over sunitinib [95% CI, 0.49-0.88; P = .005].7 Virtually all these therapies are sitting in that 0.7 to 0.8 HR with long follow-up. In fact, the 5-year follow-up with ipilimumab plus nivolumab is sitting at 0.72. This was an earlier analysis, so it’s showing better, but it does climb into the 0.7 range [HR, 0.72; 95% CI, 0.55-0.93] with the 33.7-month median follow-up data, which were presented at the Kidney Cancer Research Summit in 2021, but the median OS hadn’t been reached.8

For the ORRs, there is a high CR rate of 16.1% for the lenvatinib-plus-pembrolizumab arm, with a very low progressive disease rate. So roughly 94.6% of patients having at least stable disease—that’s the clinical benefit rate. It is very striking to give a therapy and know on the first scan that there’s a 95% chance they’re at least going to have stable disease. So one can choose it and feel comfortable that there’s going to be at least that level of activity.

The median duration of response that’s been shown so far is 25.8 months in those that are responding; 79% maintained a CR at 24 months, and 74% maintained a CR at 36 months.7 We need to see the durability at 60 months when compared with the ipilimumab-plus-nivolumab data, and we just don’t have that yet. It still looks good at 36 months, but you’re losing the patients and getting CRs that are failing over time.

What toxicities should be highlighted from this treatment?

Based on treatment exposure, safety, and discontinuation, lenvatinib plus pembrolizumab is a very tolerable regimen, although it does require some work on both the patient’s side and the physician’s side. The adverse effects [AEs] need to be handled because almost 100% of people are going to have treatment-related AEs, and those greater than or equal to grade 3 are over 80%. One then needs to consider dose reductions. And in the trial, the lenvatinib-plus-pembrolizumab group had roughly 70%, or two-thirds, of patients dose reducing. So one goes into the study starting at 20 mg, but with the recognition that two-thirds of the time you’re going to have to lower the dose.7

Toxicities are handled by dose interruption and dose reduction. If done, one can keep most patients on the regimen. So although [70% of people require] dose reductions, the majority can stay on therapy at a lower dose and continue to get benefit. Remember, we are comparing a combination regimen with a single agent, so you do get a slight increase in toxicity, but it’s not overwhelming. Grade 3 or 4 toxicities are a little bit more [frequent] with the lenvatinib plus pembrolizumab, but not drastically so.7 There is added toxicity with the combination, but it’s still within a reasonable range, given the amount of efficacy benefit you get with the therapy.

Are you familiar with the recommended dosages for lenvatinib?

I was fortunate enough to be good friends with Robert J. Motzer, [MD, of MSKCC], and he called me up years ago when E7090, which was lenvatinib, was entering its phase 1 trial. We did the phase 1 trial with it plus everolimus back then. So I was involved a little bit with the pharmacology and the drug development. It was shown that the higher the dose, the better it inhibits the FGFR pathway.

One of the reasons we think lenvatinib does so well in its mechanism of action and in resistant patients is because it inhibits FGFR. So there’s this dose response of wanting to try to hit 20 mg. There was also a phase 2 study performed by Dr Sumanta K. Pal, [MD, of City of Hope,] that was presented this past year and a half, where they looked at lenvatinib plus everolimus, and they tried to compare outcomes of starting lenvatinib at 14 mg vs 18 mg.7 They found that 14 mg was inferior to just starting at the higher dose and going down. With all that said, the theory of inhibiting receptors plus the clinical data suggests a dose response, so the thought is to try to get most of your patients to start at 20 mg.

To be honest with you, if you start at a lower dose, it’s hard to go up. One could go up in some, but some are having AEs, and they wouldn’t want to go up. So I find it better to start up and then go down. Don’t wait for the patient to be miserable. Inform them ahead of time that the reason you’re doing this is to try to get optimal shrinkage. Then most of the time, they’re good with that. The way it’s dosed down is 20 mg to 14 mg to 10 mg to 8 mg; then after completion of 2 years, pembrolizumab is discontinued, and then the patient stays on lenvatinib until progressive disease or...
toxicity—although people are entertaining the idea that patients with near-CRs or prolonged durable responses can have lenvatinib scaled back too. That’s an area of ongoing study. The dosage forms are the 4-mg and 10-mg capsules.

What data support the use of nivolumab plus cabozantinib in frontline therapy for advanced clear cell RCC?

The CheckMate 9ER study uses the other newer regimen that’s come out in the past year. It was an international study with 650 patients with untreated, advanced, or metastatic clear cell RCC. Like the other IO-plus-TKI trials, it involves all IMDC risk groups, so favorable, intermediate, and poor. Stratifications were based upon that, as well as tumor PD-L1 expression and geographic region. The randomization is 1:1, with 240 mg of intravenous nivolumab every 2 weeks and 40 mg of oral cabozantinib. Sunitinib was the traditional dose of 50 mg daily on the 4-weeks-on-and-2-weeks-off schedule. The primary end point was PFS, and secondary end points were OS, ORR, and safety. They presented their median follow-up data at the earliest time point of any of the trials after an 18.1-month median follow-up.

What are your reactions to these data?

The PFS is striking, and there’s a clear separation of the curves [when you look at the data presented as a graph]. The median PFS after 18.1 months of follow-up was 16.6 months for the combination vs 8.3 months for sunitinib [HR, 0.51; 95% CI, 0.41-0.64; P < .0001]. The 33-month median follow-up was reported recently at the February 2022 Genitourinary Cancers Symposium by Toni K. Choueiri, [MD, of Dana-Farber Cancer Institute], and the PFS was again 16.6 months vs 8.3 months [HR, 0.56; 95% CI, 0.46-0.68].

There is a little better benefit with the combination in patients with bone metastases. Whether patients had nephrectomy or not, there was a benefit, so it seems it was similar across the other IO plus TKIs in that regard. For the OS at 24 months, there is an absolute 10% improvement in survival, and the OS after a 33-month follow-up was 37.7 months for the combination and 34.3 months for sunitinib [HR, 0.70; 95% CI, 0.55-0.90]. Remember, lenvatinib plus pembrolizumab had a hazard ratio 0.72 after a 33-month follow-up, and then the hazard ratio was 0.72 at the 60-month follow-up for ipilimumab plus nivolumab, which is again in that range. The question is what happens over time.

For ORR, there is a difference in the CR and PR rates. If you add stable disease into that, you’re getting close to a 90% clinical benefit rate. The CR rate was 8% for the combination vs 4.6% with sunitinib, and it was a statistically significant difference. The median duration of response was 20.2 months for the combination and 11.5 months for sunitinib. The median time to response was 2.8 months for the combination and 4.2 months for sunitinib.

The treatment discontinuation rate was lower with the combination than it was with sunitinib [Table]. [More patients on the combination] had at least 1 dose reduction [compared with] sunitinib. It wasn’t as high as the 70% we saw with lenvatinib plus pembrolizumab, but there are a fair number of patients, almost 60%, who required a dose reduction. Like with lenvatinib plus pembrolizumab, dose reductions and dose interruptions were the main means of handling AEs. If dose reduction was done, the discontinuation rate of nivolumab plus cabozantinib was like that of lenvatinib plus pembrolizumab.

### Table. Phase 3 CheckMate 9ER Safety Results

<table>
<thead>
<tr>
<th>MINIMUM FOLLOW-UP OF 10.6 MONTHS</th>
<th>NIVOLUMAB + CABOZANTINIB (n = 320)</th>
<th>SUNITINIB (n = 320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of therapy (range), months</td>
<td>14.3 (0.2-27.3)</td>
<td>14.3 (0.2-27.3)</td>
</tr>
<tr>
<td>Patients with at least 1 dose reduction, %</td>
<td>56.3</td>
<td>51.6</td>
</tr>
<tr>
<td>Treatment discontinuation, %</td>
<td>44.4</td>
<td>71.3</td>
</tr>
<tr>
<td>Treatment discontinuation due to disease progression, %</td>
<td>27.8</td>
<td>48.1</td>
</tr>
<tr>
<td>Any grade treatment-related AEs leading to discontinuation, %</td>
<td>15.3</td>
<td>8.8</td>
</tr>
<tr>
<td>–Nivolumab only</td>
<td>5.6</td>
<td>-</td>
</tr>
<tr>
<td>–Cabozantinib only</td>
<td>6.6</td>
<td>-</td>
</tr>
<tr>
<td>–Nivolumab + cabozantinib</td>
<td>3.1</td>
<td>-</td>
</tr>
</tbody>
</table>

AEs, adverse events.
**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**¹

**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.²*

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 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.

This 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.

Assessed by an Independent Review Committee.

Kaplan-Meier estimates.

Due 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.

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)

<table>
<thead>
<tr>
<th>2L (n=35)</th>
<th>3L+ (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who had received 1 prior therapy</td>
<td>Patients who had received 2 or more prior therapies</td>
</tr>
<tr>
<td>43% CR</td>
<td>28% CR</td>
</tr>
<tr>
<td>63% ORR (n=22; 95% CI: 45%, 79%)</td>
<td>44% ORR (n=16; 95% CI: 28%, 62%)</td>
</tr>
<tr>
<td>20% PR</td>
<td>17% PR</td>
</tr>
</tbody>
</table>

**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) |

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
</tr>
</tbody>
</table>
REACH FOR MONJUVI

MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant1

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 (4%), and infections (27%).

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.

Premeedicate 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 37% of patients.

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

**Infections**

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

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

**Embro-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 the 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 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>
<thead>
<tr>
<th>MONJUVI (N=81)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction</strong></td>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Fatigue*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral edema</td>
</tr>
<tr>
<td></td>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal pain*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td><strong>Infections</strong></td>
<td>Respiratory tract infection+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary tract infection†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchitis</td>
</tr>
<tr>
<td></td>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Decreased appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypokalemia</td>
</tr>
<tr>
<td></td>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Black pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle spasms</td>
</tr>
<tr>
<td></td>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pruritus</td>
</tr>
</tbody>
</table>

*Fatigue includes asthma 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: hypoplasia (6%)
- Abdominal pain includes abdominal pain, abdominal pain lower, and abdominal pain upper

For full prescribing information, please be sure to rename to “MONJUVI RC US TAF”.
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>MONJUVI¹</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>34</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time increased</td>
<td>46</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

¹The 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-induced 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. Deferring 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. Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

Refer to the lenalidomide prescribing information for recommendations.

Pediatric Use

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

Geriatric Use

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

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full Prescribing Information.
Roundtable Discussion:
Reviewing Management Options for a Patient With TNBC

CASE SUMMARY

A 48-year-old woman with T1N1 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 showed alanine aminotransferase, 1.5 times upper limit of normal (ULN); aspartate aminotransferase level, 1.5 times ULN. A CT scan showed 1 liver lesion and 2 left lung lesions. Biopsy of the liver lesion confirmed recurrent metastatic TNBC, and her brain MRI was negative for brain metastasis. Genetic panel testing was negative for detectable mutations. The PD-L1 on immune cells (Ventana PD-L1 [SP142] assay) was 0%. There were no significant comorbidities, and she was otherwise healthy. She had an ECOG performance status of 0.

POLLING QUESTION

“Which frontline therapy would you recommend for this patient with metastatic recurrence 8 months after adjuvant dose-dense doxorubicin and cyclophosphamide plus paclitaxel for her TNBC?”

- Clinical trial 50% (4)
- Combination chemotherapy 25% (2)
- Oral single-agent chemotherapy 12% (1)
- Other 12% (1)
- Intravenous single-agent chemotherapy 0% (0)

Total votes: 8

CONLIN: Is the oral single-agent therapy capecitabine?

BORKOWSKI: That’s what I thought.

CONLIN: It’s so recent since her taxane. Were people thinking about another option? Anything special?

CHAUNCEY: I’m coming from the [perspective] that I don’t see a lot of these cases, but this is a lot of chemotherapy up front and it’s only 8 months, so [I would go for] a trial. If you don’t have a trial, then something different.

CONLIN: So you feel like she didn’t have a lot of chemotherapy responsiveness. What else?

CHAUNCEY: She’s young, and she only had 8 months of treatment. A platinum therapy could be different, but how different is it?

CONLIN: That’s a good point. You are trying to think outside the box for her other options, so hopefully a trial in that case.

CHAUNCEY: I am thinking about repeating the taxane.
CONLIN: So, going back to a taxane because it has been 24 months. Presumably capecitabine is still an option.

BORKOWSKI: I was leaning toward clinical trial, and I always like that capecitabine is easy. It would be something to try, depending on how much she was ready to jump into combination chemotherapy.

CONLIN: That’s a good option.

The patient received frontline carboplatin plus gemcitabine, with a documented partial response lasting 6 months. After 6 months of therapy, she reported worsening fatigue. Disease progression and a new metastasis in the liver were discovered. Her ECOG performance status was 1.

CONLIN: Let’s assume her liver numbers still look fairly good, and she has a lot of healthy liver left to tolerate another line of therapy.

CONLIN: How about if, with second-line therapy, she does respond to some chemotherapy, and you feel like she is a little more sensitive? What would you give then?

GOLDBERG: I’d join the majority and give sacituzumab govitecan. I would give that, probably holding the clinical trial next.

CONLIN: I’m surprised we didn’t get any eribulin votes, but that’s OK.

SHENOI: I chose sacituzumab. It’s the new kid on the block, has a lot of good data, and is exactly the second line to give after progression. The data explain why we need to choose that drug, and I chose it.

CONLIN: Oncologists think the ideal sequence is a chemotherapy, then sacituzumab. If you don’t have a clinical trial, I think gemcitabine plus carboplatin seems reasonable [for first-line therapy] because the patient hasn’t had platinum therapy. Then think about sacituzumab [for second-line therapy]. I think we mentioned she didn’t have a BRCA mutation.

CHINTAPATLA: I had an experience with sacituzumab in 2 patients. Both tolerated the treatment well, with response within a few months. The only thing I would say is that if patients have liver metastasis and elevated liver function tests, they seem to have a little more toxicity in terms of the cytopenia compared with patients without liver metastasis. I don’t know [whether] that is documented.

CONLIN: Did you have to do any dose reductions in those patients?

CHINTAPATLA: Yes, I did for 1 patient due to cytopenia.
CONLIN: Does anyone ever use growth factor support with sacituzumab?

WANG: I have tried to, but it was not approved by insurance. I think the guidelines say the patient must have a neutropenic fever, but it was not approved.

CONLIN: So in that case, did you dose reduce instead?

WANG: I didn’t [at first]. My patient had a tough time. She was tolerating all the previous chemotherapy very well, but this was a tough drug for her, so she was having diarrhea and prolonged neutropenia, and I think she was hospitalized for the diarrhea. The toxicities were worse than I was prepared for.

CONLIN: It sounds like she was heavily pretreated, but yes, she also struggled with the treatment.

WANG: I eventually had to dose reduce for various reasons—mostly for fatigue and diarrhea.

YAN: My experience has been pretty good. I have treated quite a few patients with sacituzumab govitecan. I was fortunate that it was approved for 1 patient as [second]-line therapy after the KEYNOTE-522 [NCT03036488] regimen.

The other patient had TNBC heavily treated with a lot of monotherapies, and quite a few were mixed. They had a lot of alopecia, and because it’s an ADC [antibody-drug conjugate], I was not prepared for the grade 3 alopecia. For neutropenia, I had pegfilgrastim [Neulasta] approved on day 8, so it was never an issue for me. So far, I have not had to dose reduce sacituzumab.

CONLIN: So you have used a long-acting [granulocyte colony-stimulating factor] on day 8 and not had to dose reduce. Are you doing that for everybody or just depending on the patient’s [response]?

YAN: It depends on the patients. I do not get it approved up front, I wait. From my experience, for a lot of my patients, I don’t do day 8 treatment. Although day 8 neutropenia is common, I have been scheduling them at around day 10. That’s when the neutropenia can recover. I have a lot of patients tell me they must come back a day or 2 after day 8, so I tell them not to come back on day 8 but on day 10 or 11, and it has been working out for me. When they have repetitive neutropenia, I can get pegfilgrastim approved, so I never need to reduce the dose because of neutropenia. I dose reduce for other reasons, but not for neutropenia.

CONLIN: Have you had struggles with diarrhea, as well, or not so much?

YAN: Not so much. I did have 1 patient with TNBC who had diarrhea previously from other regimens, so when diarrhea happened, she did not even blink on this treatment. I gave her a lot of diphenoxylate/atropine [Lomotil] and she was fine. Diarrhea can happen, but we are oncologists, and I feel we can manage that.

CONLIN: I have not seen so much of the diarrhea, just like you. Maybe some of these patients are already prepared on what to use for diarrhea. Initially, I was a little surprised about nausea. I find we always assume we are not going to see nausea [with ADCs], now we know that’s not nearly the case.

I have had patients with a little neutropenia and other hematologic toxicities. I don’t think I’ve had to use as much growth factor support, but I am probably more likely to maybe hold or dose reduce, but growth factor support seems like a good option.

YAN: Yes, this is exactly why I am an advocate for using growth factor therapy earlier rather than later, because if the patient is heavily treated, adverse effects [AEs] are more common. But if they are not heavily treated, then AEs are not as common.

DISCUSSION QUESTIONS

- What do you think of the outcomes of the phase 3 ASCENT trial (NCT02574455) of sacituzumab govitecan in the context of other therapies commonly used in the setting of relapsed/refractory metastatic TNBC?

- Have you used sacituzumab govitecan in the second-line metastatic setting?

- Would you use it earlier than the third-line setting?

CHAUNCEY: In the ASCENT study, did patients stop the drug at the time of progression?

CONLIN: Yes.

CHAUNCEY: It seems like there’s a disconnect, or maybe I am not used to looking at this group of patients in a trial. But the OS [overall survival] benefit was profound, even though the PFS [progression-free survival] was less so, and it was persistent [median PFS, 5.6 months vs 1.7 months; median OS, 12.1 months vs 6.7 months].

1, 2
Did the patients who progressed get other treatment? Did this somehow potentiate the treatment beyond stopping the drug?

**CONLIN:** Those are good questions and observations. I think patients who potentially don’t respond may die quickly. I think we see this with patients. We can’t even get a next line of therapy before they end up having liver or respiratory failure. [It happens] before you get something approved. So those who aren’t responding are making that difference, potentially. It is a good question. When there is crossover, it’s not planned, and patients have access to other things, you don’t know where the survival benefit is from.

**CHAUNCEY:** There is a big difference in OS.

**DISCUSSION QUESTION**

What is your overall approach to molecular testing after metastatic relapse or progression?

**CONLIN:** In our case, the patient had a biopsy when she first presented. Are you getting any special molecular testing, or doing biopsies on all patients? Will everybody share what they generally do when patients present with metastatic disease?

I try to biopsy my patients and do some molecular testing to look for TNBC and PD-L1 expression, but also any targetable mutations and their BRCA mutational status.

**GOLDBERG:** Overall, we are getting much more aggressive in testing now. Hopefully insurance gives us the OK, but it’s getting to be a necessity. [We send out to] FoundationOne and [Tempus].

**CHINTAPATLA:** We test on a routine basis—mostly [next-generation sequencing] to the Providence [St Joseph Health Molecular Genomics Laboratory].

**DISCUSSION QUESTIONS**

- What is the value of potential biomarkers to guide the use of sacituzumab govitecan (eg, Trop-2 expression, germline-mutation status)?
- What are you using most often as next-line therapy for progression on or after sacituzumab govitecan?

**CONLIN:** [Sicituzumab] is an ADC targeted to Trop-2, and of the patients on the trial, [approximately] 80% or so had Trop-2 expression. [However], we are not sure whether that seemed to be the selection of the population that needed it. I am not sure I’ve seen that kind of testing anywhere.

Is anyone doing any trials on this or have anything they want to share on this?

**YAN:** No, [Trop-2 testing] does not help at all. We can test for that if we want to, but I do not feel it helps me with any decisions, so I don’t send them.

**CONLIN:** Right, so you aren’t sending it for your practice. Let’s say the patient gets gemcitabine plus carboplatin first because it is a short sequence, then sacituzumab. What would be the thing you might use after?

**CHINTAPATLA:** Capecitabine [would be] my other option.

**CONLIN:** It probably depends a lot on what is going on with the patient. If they are having rapidly progressive liver disease, what is safe to give them in terms of dosing? If they need a break from coming in all the time, maybe capecitabine is a nice option for when people want to not be there as much, physically sitting in the chairs.

**SHENOI:** If the patient was BRCA positive with metastasis, would you consider olaparib [Lynparza] plus carboplatin?

**CONLIN:** There are [data for] the olaparib plus carboplatin regimen, but I haven’t given them together. Olaparib is a nice option for patients. It is oral, but it does have a toxicity profile that is not completely benign, with hematologic toxicities, fatigue, and nausea, as well. But again, it depends on how sick a patient is or how quickly I feel like I need a response. But it feels like a good thing for patients, [for you] to be able to say, “I have a target on the tumor that we can address with a PARP inhibitor.” So, I might start with it sooner.

**DISCUSSION QUESTION**

Which efficacy end points are most meaningful (OS, PFS, overall response rate, time to response, duration of response, etc)?

**GOLDBERG:** They are all important when you are getting to this point. You must put the whole patient together again, and quality of life [QOL] is No. 1, then you think about selecting something with the best chance without significant burdening of the patient. Because chances are, with third-line therapy, you are not making big home runs here. I think OS and PFS, but QOL is important, too, so you must weigh that with what you are going to try.
People think the ideal sequence is a chemotherapy, then sacituzumab. If you don’t have a clinical trial, I think gemcitabine plus carboplatin seems reasonable [for first-line therapy] because the patient hasn’t had platinum therapy. Then think about sacituzumab [for second-line therapy].”

—ALISON K. CONLIN, MD

CONLIN: Do you worry about the patients’ age or their other comorbidities? Does that factor in for you, as well?

GOLDBERG: Performance status is in there, [as well as] frailty, which would cover all the other comorbidities and factors like that. If they have a certain comorbidity that would be, for a certain drug, detrimental going forward, [then] yes. One must then weigh QOL and toxicity of each drug, so when you go to a third-line option, you are more flexible. That’s why capecitabine is a nice drug. I almost think it’s the hospice drug. We all use it because it’s so easy, and I’m not sure whether we are doing anything [for the disease] on third-line therapy. It would be nice to have third-line trials, except clinical trials of third-line agents don’t look too good either, because patients have been [through a lot]. It’s a complex decision.

CONLIN: I agree. You are hitting on a lot of important points. For capecitabine, we all know what you mean. The other point about trials in the third-line setting is that people who have these great performance statuses on third-line therapy [might] have a special type of TNBC. Those might be a different selection of people in the real world. How easy is it to have someone who can wait 3 weeks to get the tests done, have good laboratory results, and have all the good stuff that gets you on the study? If we get those patients, we certainly want to have the data show great options for them.

WANG: I agree and disagree, because everyone is different in a way that is not just age, performance status, or QOL. That matters the most for me. I have some patients who—if you hold chemotherapy for 1 week, we have all the disease coming out and it is out of control—I absolutely cannot allow to go on vacation for a week because it will be out of control. I have another patient with metastatic TNBC who has survived for 5 years, so far. There are outliers.

I am looking at my patients and asking them and myself whether we have the luxury to wait and [whether] they have a relatively [stable] disease—or we don’t even have the luxury to wait for 1 week. So when it comes to third-line therapy and you don’t have the luxury to miss the androgen receptor [but] I have the luxury to send for genomic tests, then I can be creative. There are some patients—because it’s so aggressive as a continuous chemotherapy—who can never take any breaks. Some patients feel better with chemotherapy because the cancer is giving all the symptoms.

REFERENCES

Case-Based Roundtable Series

For more case-based articles and videos, scan the QR code or go to TargetedOnc.com/link/1535.
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 trial¹³

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, ie, 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

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 Rd 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)1

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 asthma

- 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

Efficacy results in long-term follow-up

At median ~5 years (56 months)1 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

- Most frequent TEAEs≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

- Grade 3/4 infections were 41% for DRd vs 29% for Rd

- Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5-year analyses are not included in the current Prescribing Information.

-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 these 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, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®. Consider administering...
corticosteroids and other medications after the administration of DARZALEX® and DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions. 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 daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX® and DARZALEX FASPRO® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX® FASPRO®.

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: 0 minutes to 6.5 days) after starting administration of DARZALEX® FASPRO®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX FASPRO® may increase neutropenia 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 FASPRO® until recovery of neutrophils or for recovery of platelets. In lower body weight patients receiving DARZALEX® FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX FASPRO®: Interference With Determination of Complete Response

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. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX® and DARZALEX FASPRO®.

DARZALEX® and DARZALEX FASPRO®: 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 FASPRO®: Embryo-Fetal Toxicity

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

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX FASPRO®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dysgeusia, 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 FASPRO® are decreased leukocytes, 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 eligible 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 FASPRO® (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 eligible for autologous stem cell transplant
• In combination with lenalidomide and dexamethasone in newly diagnosed patients who are eligible 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 FASPRO® on adjacent pages.

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

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 for ASCT was that 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 EQUEULEUS, 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 reaction was 22%, with 38% of patients experiencing infusion-related reactions on Day 1 of Week 1, 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-medicate 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 reaction (Grade 4) 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 patients, 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 depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX 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 lenalidomide, pomalidomide, or thalidomide in clinical trials. 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 lenalidomide, pomalidomide, or thalidomide in clinical trials. 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.

ADVERSE REACTIONS
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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 60.64 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 DRd 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>DRd (N=364)</th>
<th>Rd (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection a</td>
<td>52</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Bronchitis b</td>
<td>29</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia a</td>
<td>26</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions a</td>
<td>41</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Peripheral edema a</td>
<td>41</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>32</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>34</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Muscle spasm s</td>
<td>29</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea a</td>
<td>32</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cough b</td>
<td>30</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>14</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension c</td>
<td>13</td>
<td>6</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Key: D=daratumabum, Rd=lenalidomide-dexamethasone.

### Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
<td>5</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
<td>7</td>
<td>17</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
</tbody>
</table>

### 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>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 1 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection a</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea a</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Cough c</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory tract infection b</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 4: Adverse Reactions Resulting in Discontinuation

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 1 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection a</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea a</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Cough c</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory tract infection b</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

Key: D=daratumab, Rd=lenalidomide-dexamethasone.

### Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX [see Clinical Studies (14.2) in Full Prescribing Information]. Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.
**DARZALEX® (daratumumab) injection**

### 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>42</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>92</td>
<td>36</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.

**Hepatitis Zoster Virus Reactivation**

Prophylaxis for Hepatitis Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2.5% of patients receiving DARZALEX.

**Infections**

Grade 3 or 4 infections were reported as follows:

- a where carfilzomib 20/50 mg/m² was administered twice-weekly
- b where carfilzomib 20/70 mg/m² was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%; VMP: 15%; DRd: 32%; Rd: 23%; DdT: 22%; VdT: 26%

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1.4% of patients.

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%; Vd: 2%; DRd: 2%; Rd: 1%; DdT: 2%; Dkdt: 5%; Dkdt: 3%; Dkdt: 0%
- a where carfilzomib 20/50 mg/m² was administered twice-weekly
- b where carfilzomib 20/70 mg/m² was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%; VMP: 1%; DRd: 2%; Rd: 2%; DdT: 0%; VdT: 0%

Fungal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fungal 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 in 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 DARZALEX 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, Listeriosis

**DRUG INTERACTIONS**

### Effects of Daratumumab on Laboratory Tests

**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**

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.

**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. Refer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematologic evaluation is completed.

**Data**

**Animal Data**

Mice that were genetically modified to eliminate all CD38 expression (CD38−/−) showed diminished maternal tolerance (mice), and early embryonic development (frogs). The involvement of CD38 in regulating humoral immune responses (mice), fetal development (frogs), and 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 additional information.

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

Infusion-Related Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chill, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing [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 notice signs of bruising or bleeding [see Warnings and Precautions].

Interference with Laboratory Tests
Advise 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]. Advise patients that DARZALEX 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 could cause hepatitis B virus to become active again [see Adverse Reactions].

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].

Hereditary Fructose Intolerance (HFI)
DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol [see Description (11) in Full Prescribing Information].
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX FASPRO 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 FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO (see Adverse Reactions).

Systemic Reactions

In a pooled safety population of 888 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2-3: 7%, Grade 3-4: 2%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 1% with the second injection, and dexamethasone, respectively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 35 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.

Serious reactions include hypoxia, dyspnea, hypertension, and 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; anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetylaminoephene and corticosteroids (see Dosage and Administration (2.5) in Full Prescribing Information). Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.5) in Full Prescribing Information).

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusion with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

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: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib and dexamethasone (see Adverse Reactions). Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to the 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).

Non-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.

Dose interruptions due to an adverse reaction occurred in 83% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, interstitial lung disease, and blood creatine 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.
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>52</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
</tr>
<tr>
<td>Gastrointestinal disorders</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>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionb</td>
<td>43</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>23</td>
</tr>
<tr>
<td>Bronchitisc</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spasmss</td>
<td>31</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspneaæ</td>
<td>22</td>
</tr>
<tr>
<td>Coughf</td>
<td>14</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
</tr>
</tbody>
</table>

- Fatigue includes asthenia, and fatigue.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial. 
- Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
- Bronchitis includes bronchitis and bronchitis viral.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Cough includes cough, and productive cough.
- 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: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
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<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>88</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
</tr>
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</table>

- Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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) formation 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 below described with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 812 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience
The following adverse reactions have been identified with 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: Anaphylactic reaction, Systemic administration reactions (including death)
Gastrointestinal: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS
Effects of Daratumumab on Laboratory Tests
Interference with Indirect Antibody 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 AB-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 DARZALEX FASPRO-treated 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
DARZALEX FASPRO 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 FASPRO 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 major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

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- Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).
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 density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero daily during organogenesis, which is 134 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 embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously 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.

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 291 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 weight loss, hyperglycemia, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia, urinary tract infection, and peripheral edema.

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 193 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, 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
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cp-267681v2
Roundtable Discussion: Abou-Alfa Evaluates Choice of Therapy for HCC Based on Patient Factors

CASE SUMMARY

A 77-year-old White woman presented to her primary care physician complaining of abdominal pain and fatigue. She had a medical history of cirrhosis due to heavy alcohol use, Crohn disease controlled with infliximab (Avsola), and variceal bleeding with banding 2 months ago. Her ECOG performance status was 1. A CT scan of the chest, abdomen, and pelvis with triphasic liver evaluation showed a 4.5-cm hepatic mass in the right lobe plus metastatic disease in the lung. Her Liver Imaging Reporting and Data System (LI-RADS) score was 5 (LR5). She had a Child-Pugh score of A, and her α-fetoprotein (AFP) level was 380 ng/mL.

DISCUSSION QUESTIONS

• Would your use of biopsy be different if the patient did not have cirrhosis?
  ◦ Would it differ if the lesion were LR4?

• Assuming biopsy was obtained and confirmed hepatocellular carcinoma (HCC), would you suggest any further genetic analysis of the biopsy tissue?

• Would you recommend any further imaging?

SIDDQUI: If [the LI-RADS score was] 4, I [would] probably do a biopsy. The other [possible] benefit of biopsy is next-generation sequencing [NGS], but I’m not sure if NGS is very helpful in HCC.

ABOU-ALFA: That is a great point that you bring up. [There are] a few points [to consider] about the biopsy. [Concerning] LI-RADS...I spoke with the radiologist who wrote the final LI-RADS radiologic assessments.

I got [what is] probably the best answer from him. He [said that] when [medical oncologists] talk to each other, one can say, “I have a patient with stage IV disease,” and the other one will understand that the disease is not resectable, it’s not curable, [and so on]. Interestingly, the LI-RADS [score works similarly] for radiologists. They can say, “I have a patient with an LR5 lesion,” [and] their mindset is that this is probably HCC. I asked the very direct question [of whether they would] be ready to say that a patient had HCC [on the basis of] the radiological assessment by itself. And the answer was no, because sometimes those can very much [indicate] other things [such as] cholangiocarcinoma.

A patient can have combined cholangiocarcinoma and HCC, which can happen in up to 15% of patients. And interestingly, some other things [besides HCC] can [produce] high AFP. So I think we’re obligated to get a diagnosis to know what’s going on [with] the patient. Almost all the clinical trials that were done in HCC were biopsy driven; nothing was done radiologically.

[Point] No. 2 is that with regard to genetic testing, it’s not like we have too many options to offer the patients. But if we don’t do the testing and learn from it, we’ll never be able to tell what the story is. Can we see certain genetic alterations that can be applicable in
HCC? Yes, we can. We have seen alterations, for example, in FGFR2, FGFR4, FGF19, and IHD1. So it’s not only in cholangiocarcinoma; it can happen in HCC as well. I strongly recommend to you to do a biopsy at all times.

[At] Memorial Sloan Kettering Cancer Center, when a patient comes in, we get a biopsy [and] we send it to a pathologist to be reviewed. At the same time, we will do genetic testing, exactly as we just discussed. On top of that, believe it or not, we take a sliver of that tissue…and we’ll send it immediately [and] embed it in mice for a patient-derived xenograft mouse model.

We’ll learn a lot from the patient’s disease, and we can offer the patient better therapy. And that’s why, with all those options in front of us, it will be important that we develop a better understanding of the tumor. My recommendation is, by all means [do] the biopsy. I think it will be the right thing for patients, and let’s not depend, as medical oncologists, on the LI-RADS testing, which is not enough for that purpose.

**CASE UPDATE**

A biopsy was obtained and confirmed the diagnosis of HCC.

**POLLING QUESTION**

“Considering the American Joint Committee on Cancer stage IV disease, Child-Pugh A status, and cirrhosis, what frontline therapy are you most likely to recommend for this patient?”

- Atezolizumab plus bevacizumab: 70% (7)
- Lenvatinib: 30% (3)
- FOLFOX: 0% (0)
- Nivolumab: 0% (0)
- Sorafenib: 0% (0)
- Other: 0% (0)

Total votes: 10

**DISCUSSION QUESTION**

Which key factors would you consider in selecting frontline therapy for this patient: age, gender, etiology of cirrhosis, anticipated toxicity/tolerance, comorbidities, performance status, Child-Pugh status, or other?

**ABOU-ALFA:** [The patient] had Crohn disease, and she [also] bled from varices and she had banding 2 months ago. My question is, with varices, what’s your comfort zone? [At what point do] you think you can give bevacizumab [Avastin]? [Do you not wait] at all, wait 2 months, 4 months, 6 months, or 1 year?

**SIDDQUI:** I think it should be a couple of months.

**ABOU-ALFA:** In other words, 2 months is enough? I have to admit, I’d be worried. The comfort zone, [based] on the IMbrave150 study [NCT03434379], is 6 months.¹ So [to give] bevacizumab within 2 months after variceal [banding is] not a good idea. If you remember, [when] bevacizumab [was investigated] as a single-agent therapy for HCC, [a patient died from a fatal variceal bleed].² I urge you not to fiddle in that arena, because patients can get hurt from potential bleeding.

Any comment in regard to the Crohn disease? How much does it worry you with regard to atezolizumab [Tecentriq] and bevacizumab?

**BENDALY:** I would be worried, especially if [the patient were] on immunosuppressive treatment. I don’t know how it would interfere with the activity of immunotherapy.

**ABOU-ALFA:** Yes. That’s very true. I personally would agree with you. But on the other hand, you might very well [choose to] send the patient to the gastroenterologist and let them assess [the situation]. If the Crohn disease has been rather stable, [with] no events, [you might choose] close monitoring. I [could] understand that. So the varices would [definitely rule out] the bevacizumab, and the Crohn disease [might rule out] the atezolizumab. [The decision about using atezolizumab could] probably [go] either way. I would be rather cautious. This is the point: Atezolizumab plus bevacizumab, as great as [this combination] is, is not a choice for everybody. And probably in this specific patient, with relative concern about the Crohn disease but more critical concern about the varices, I would urge you not to give atezolizumab plus bevacizumab here. If anything, I [would choose] to give lenvatinib [Lenvima]. That is probably the right option for this patient.

**SINGH:** I think, realistically, all of them [are important], but my top 4 would be etiology of the cirrhosis, comorbidities, performance status, and Child-Pugh status.

**ABOU-ALFA:** I agree with what you said, and I like very much what you said in the beginning, which is [that] truly, they all apply. But I’m curious about 1 thing: you mentioned the etiology. [Do you choose 1 therapy over another on the basis of etiology] (hepatitis B, hepatitis C, or nonviral [hepatitis])?

**SINGH:** I think it’s more of a curiosity, because I know that in the study of atezolizumab plus bevacizumab,
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they did have a significant portion of patients, who were hepatitis B positive. Those patients had a more positive response. So if you know that is the etiology of their cirrhosis, [and] they otherwise don’t have any variceal bleeding, [and] you think they can tolerate bevacizumab, [there’s] no reason why [they couldn’t] have immunotherapy. [This line of thinking] guides me toward a regimen of atezolizumab plus bevacizumab in those patients with hepatitis B.

ABOU-ALFA: You’re absolutely right. About 40% to 50% of patients in the IMbrave 150 [study] had hepatitis B. And we know very well that patients with hepatitis B can fare better on immunotherapy, independently of what immunotherapy you give. [Those faring next best were] the patients with hepatitis C, followed by those with nonviral hepatitis. But [it is] very important [to note that this] does not mean that the patient with hepatitis C and the patient with nonviral hepatitis will not benefit. Everybody will benefit but, as you said, [there may be] a bit more [benefit] for the patients with hepatitis B than for the others. Yes, out of curiosity, I too like to know the etiology, but I would not make the [therapeutic] decision based on the [etiology]. [Etiology] might play a role in the future, though we’re not there yet, but I like your analysis.

The patient began treatment with 12 mg of lenvatinib (Lenvima) daily. She experienced modest weight loss and reported loss of appetite, leading to a dose reduction to 8 mg daily. The patient was referred for nutritional therapy. Imaging at 16 weeks revealed a partial response. Eight months after initiation of therapy, treatment was discontinued due to disease progression.

ABOU-ALFA: We probably all see [cases like this one]. Does this reflect the experience that you have had with lenvatinib, or have you had a different experience?

TAJUDDIN: I don’t have experience with lenvatinib in this situation, but I have used it in metastatic thyroid and uterine cancer. [My patient] with metastatic thyroid cancer is doing quite well with the reduced dose, and he’s responding. The [patient] with uterine [disease] is not doing so well; [this is] because of poor tolerance, especially [gastrointestinal] toxicities. [It reached] the point that she said, “I absolutely don’t want to take this drug because it’s making me feel awful.” So these are 2 different experiences that I had.

ABOU-ALFA: You hit it right on; a reasonable number of patients will end up needing dose reduction to 8 mg. But I hope after [our] discussion, you’ll join us with regard to giving lenvatinib to patients, because I think it is easily tolerated. That’s a big plus for the drug, no question about it.

ABOU-ALFA: You’re absolutely right. About 40% to 50% of patients in the IMbrave 150 [study] had hepatitis B. And we know very well that patients with hepatitis B can fare better on immunotherapy, independently of what immunotherapy you give. [Those faring next best were] the patients with hepatitis C, followed by those with nonviral hepatitis. But [it is] very important [to note that this] does not mean that the patient with hepatitis C and the patient with nonviral hepatitis will not benefit. Everybody will benefit but, as you said, [there may be] a bit more [benefit] for the patients with hepatitis B than for the others. Yes, out of curiosity, I too like to know the etiology, but I would not make the [therapeutic] decision based on the [etiology]. [Etiology] might play a role in the future, though we’re not there yet, but I like your analysis.

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DISCUSSION QUESTIONS

- How do the toxicity profiles of lenvatinib and sorafenib (Nexavar) differ when these drugs are used for unresectable HCC?
- What is your approach to adverse event (AE) prevention, monitoring, and management with each of these agents?

KU: I haven’t used lenvatinib in liver cancer, but I’m using it in other cancers like kidney cancer. I run into AEs like hypertension [and] diarrhea. I have used sorafenib in liver cancer, and I dealt with a lot of appetite and weight loss problems.

ABOU-ALFA: Yes, I think you’re right on all of that. And by the way, don’t expect the AEs to be different depending on the disease. [The things you mentioned] are the [AEs] that we expect in regard to lenvatinib. You will [also] probably see quite a bit of hand/foot syndrome [with] sorafenib. Patients don’t like sorafenib; it can cause [a lot] of AEs and can be a problem.

KOKO: I have a patient currently on lenvatinib for endometrial carcinoma, I think. Hypertension has been a problem, but she also [developed] congestive heart failure, which she never had until she was placed on lenvatinib. I’m concerned that [the lenvatinib is the cause]. I had to reduce her dose. Initially, the dose was held for a while, and then [I reduced it] to 8 mg, which she’s been tolerating well. But she was hospitalized multiple times with congestive heart failure when she was on a higher dose. Since [I reduced] the dose, she hasn’t had any further episodes.

ABOU-ALFA: Thanks so much for bringing this up; this is quite intriguing, because it’s a very uncommon AE that can occur. We have seen this with tyrosine kinase inhibitors [TKIs] across the board, and it can happen with lenvatinib, like in many others. But again, it’s not like we see it all the time. This is a very rare AE, but it does happen.

NABRINSKY: I can only reiterate what my colleagues said. And when it comes to appetite loss or taste changes, [these are] quite common, and we never know whether [they are] attributable to the disease itself or to the drug. That’s a judgment call.
TUMOR TYPE

ABOU-ALFA: I think you’re absolutely right. Those AEs can be [attributable to] both [the disease and the drug]. [And because they] can be [caused by] the drug, a reduction of dose will probably help. If you reduce the dose to 8 mg, it [can improve] the appetite. By all means, it’s something you can practice.

TAJUDDIN: Dose reduction is very common with lenvatinib, regardless of which kind of tumor you are treating. So, would it be fair to start at the lower dose or would you still want to [start with] the [original] dose intensity?

ABOU-ALFA: Let me give you a little background on this. Interestingly, the whole story about starting on a low dose started with sorafenib. The sponsor of sorafenib wanted to do it that way because they were very concerned about the hand/foot syndrome. But we’re all taught to give [chemo-therapy at the] full dose and this applies also to TKIs. No, I would not start on a lower dose; I would start on 12 mg. You’ll be surprised [to see] that patients can tolerate it, and they can do very well with it. Of course, however, I’ll have a very active role in trying to reduce the dose if I have to. I urge you all [not to] give the lenvatinib and tell the patient, “See me in a month.” You’ll probably have to see the patient in a week’s time, because AEs will happen very quickly. You want to be sure [you are monitoring the situation and watching] for any symptoms that can occur, [including] congestive heart failure, as Dr Koko [mentioned]. Close monitoring is needed, especially in the beginning.

BARAI: In any of these treatments, does it make any difference if the patient has elevated AFP, [in comparison with the] small percentage of patients with HCC who don’t have elevated AFP? Is there a difference in their responses?

ABOU-ALFA: AFP is not a prognostic marker for HCC. [Elevation of AFP] can happen for many reasons. Any inflammation of the liver, no matter [the cause], can [result in elevated] AFP, [as can] gastric cancer. It appears that [elevated] AFP might imply liver dysfunction, but it does not have any prognosticative [power]. I will check it, but I usually don’t check on a regular basis. I check regularly only on CAT scan times, and I [only] use [AFP level] as a third [consideration], after the [results of the] physical exam and the CAT scan, before I make a decision. But [you make] a great point.

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

FROM THE DATA

In the phase 3 IMbrave150 trial (NCT03434379), of 501 patients in the intent-to-treat population, 240 had hepatitis B, 108 had hepatitis C, and 153 had nonviral hepatitis. The HR for progression or death favored atezolizumab (Tecentriq) plus bevacizumab (Avastin) vs sorafenib (Nexavar) in all 3 subgroups with an HR of 0.51 (95% CI, 0.37-0.70) for the hepatitis B group, 0.68 (95% CI, 0.42-1.10) for the hepatitis C group, and 0.80 (95% CI, 0.55-1.17) for the nonviral hepatitis group.
ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.1-10

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.11

INDICATION

RYBREVANT® (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Days 1, 55% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions

RYBREVANT® can cause rash (including dermatitis acneiform), pruritus, and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
The safety of RYBREVANT® was evaluated in the CHRYSLIS* study (n=129)11:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity11
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%)
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%)
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion11

1Based on the safety population, N=302.

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If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Ocular Toxicity
RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Embryo–Fetal Toxicity
Based on its mechanism of action and findings from animal models, RYBREVANT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT®.

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Please see Brief Summary of full Prescribing Information for RYBREVANT® on subsequent pages.

References:
RYBREVANT™ (amivantamab-vmjw) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.4) in Full Prescribing Information], whose disease has progressed on or after platinum-based chemotherapy.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population [see Adverse Reactions], IRR occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 85% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset of first IRR was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended [see Dosage and Administration (2.3) in Full Prescribing Information]. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.6) in Full Prescribing Information].

Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Intestinal Lung Disease/Pneumonitis

RYBREVANT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population [see Adverse Reactions], ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (2.4) in Full Prescribing Information].

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Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Ocular Toxicity

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Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT [see Use in Specific Populations].

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

• Infusion-Related Reactions [see Warnings and Precautions]
• Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions]
• Dermatologic Adverse Reactions [see Warnings and Precautions]
• Ocular Toxicity [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 population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 22 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade ≥4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included: pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash and paronychia.

The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.
Table 1 summarizes the adverse reactions in CHRYSLIS.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVANT (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33</td>
</tr>
<tr>
<td>Edema&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain&lt;sup&gt;e&lt;/sup&gt;</td>
<td>47</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;f&lt;/sup&gt;</td>
<td>37</td>
</tr>
<tr>
<td>Cough&lt;sup&gt;g&lt;/sup&gt;</td>
<td>25</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain&lt;sup&gt;h&lt;/sup&gt;</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage&lt;sup&gt;i&lt;/sup&gt;</td>
<td>19</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy&lt;sup&gt;j&lt;/sup&gt;</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Headache&lt;sup&gt;k&lt;/sup&gt;</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema astetic, pruritus, hyperhidrosis, rash maculo-papular, rash papular, rash papular, skin exfoliation, toxic epidermal necrolysis
<sup>b</sup> Fatigue: asthenia, fatigue
<sup>c</sup> Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
<sup>d</sup> Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
<sup>e</sup> Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
<sup>f</sup> Dyspnea: dyspnea, dyspnea exertional
<sup>g</sup> Cough: cough, productive cough, upper airway cough syndrome
<sup>h</sup> Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
<sup>i</sup> Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
<sup>j</sup> Hemorrhage: epistaxis, gingival bleeding, hematoma, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
<sup>k</sup> Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
<sup>l</sup> Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

Table 2 summarizes the laboratory abnormalities in CHRYSLIS.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYBREVANT+ (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>79</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
</tr>
</tbody>
</table>

<sup>a</sup> The denominator used to calculate the rate was 126 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 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 amivantamab products may be misleading.

In CHRYSLIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in
multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

**Lactation**

**Risk Summary**

There are no data on the presence of amivantamab-vmjw in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

**Females and Males of Reproductive Potential**

RYBREVANT can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

**Pregnancy Testing**

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

**Pediatric Use**

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

**Geriatric Use**

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

**PATIENT COUNSELING INFORMATION**

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

**Infusion-Related Reactions**

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions [see Warnings and Precautions].

**Interstitial Lung Disease/Pneumonitis**

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [see Warnings and Precautions].

**Dermatologic Adverse Reactions**

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT [see Warnings and Precautions]. Advise patients to apply alcohol free emollient cream to dry skin.

**Ocular Toxicity**

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated [see Warnings and Precautions].

**Paronychia**

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia [see Adverse Reactions].

**Embryo-Fetal Toxicity**

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. [see Warnings and Precautions, Use in Specific Populations].

**Lactation**

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose [see Use in Specific Populations].

**Product of Ireland**

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**cp-213278v1**
Couriel Assesses the Available Data for Treatment of Acute GVHD

CASE

- A 48-year-old man underwent a myeloablative conditioning regimen and peripheral blood stem cell–matched hematopoietic cell transplant from an unrelated donor for acute myeloid leukemia with tacrolimus plus methotrexate (Trexall) and graft-vs-host disease (GVHD) prophylaxis.
- The donor was a cytomegalovirus (CMV) seropositive 50-year-old woman with 3 children.

Daniel R. Couriel, MD, MS, MBA
Director, Utah Blood and Marrow Transplant Program
Huntsman Cancer Institute
Salt Lake City, UT

Targeted Oncology™: What is this patient’s risk of developing acute GVHD (aGVHD)? What are other risk factors for aGVHD?

Couriel: The risk factors can be classified as donor-recipient factors, stem cell graft factors, and transplant factors. For each of these factors, specific conditions can increase the risk of aGVHD.

Donor-recipient factors include major human leukocyte antigen (HLA) disparity, mainly class I and class II, with a greater risk associated with mismatched than with matched donors. [There was also] minor HLA disparity, greater risk with unrelated than with related donors; sex matching, greater risk with mismatched than with matched donors; donor parity, with a greater risk with multiparity than with nulliparity; and donor age, greater risk with older donors than with younger donors.

[This effect of donor age] is even more truthful for certain types of transplants, like haploidentical transplants, with older donors infrequently [responding] better than younger donors. For ABO blood type, a greater risk is associated with mismatched donors than with matched donors, and for donor CMV serostatus, positivity is associated with greater risk than is negativity. Numerous cytokine gene polymorphisms have been associated with aGVHD, but the problem with [identifying] these polymorphisms is that [doing so requires many] patients, and we deal with diseases that are not [common].

Stem cell graft factors [include] the stem cell source; peripheral blood [stem cell] grafts [are associated with a greater risk than are] bone marrow grafts, which, in turn, are associated with a greater risk than are umbilical cord [blood grafts]. For graft composition, a higher CD34+ count [and a higher T-cell dose] are both more likely to cause aGVHD than are a lower CD34+ count [and a lower T-cell dose]. Finally, conditioning intensity, a transplantation factor, affects aGVHD risk, and myeloablative regimens are associated with greater risk than are reduced-intensity nonmyeloablative regimens.

CASE UPDATE

- On day 22 following transplant, the patient developed the following:
  - Maculopapular rash on his face, upper chest, forearms, shoulders, and back; estimated body surface area [BSA] involvement, 60%
  - Watery diarrhea, 4 episodes a day for 2 days

What GVHD staging and grading system is preferred for everyday use? How has organ staging been applied to risk stratification?

That preferred staging and grading system is the Mount Sinai Acute GVHD International Consortium [MAGIC] system, which is largely based on the Glucksberg system. [The MAGIC system assigns stages for] skin, liver, upper gastrointestinal [GI] tract, and lower GI tract. There are only minor differences in comparison with the Glucksberg system.¹

A GVHD risk stratification system, [based on staging and] mostly intended for clinical research, was published a few years ago by [Margaret] MacMillan, MD, MSc, from the University of Minnesota. I like the simplicity [of this system], which splits patients into standard-risk and high-risk groups.

[The standard-risk classification applies to] stage I-III skin, stage I-II GI, stage I-III skin plus stage I GI, and stage I-III skin plus stage I-IV liver, and everything else is high risk. [I think] it works nicely from a clinical research perspective.² Standard-risk and high-risk patients, [as defined by this system], exhibit dramatic

¹ Couriel Assesses the Available Data for Treatment of Acute GVHD

² Couriel Assesses the Available Data for Treatment of Acute GVHD
differences in the cumulative incidence of transplant-related mortality at 6 months at 22% [95% CI, 20%-24%] vs 44% [95% CI, 38%-50%], respectively. There are also significant response rate differences, especially the complete response [CR] rate [at 48% vs 27%, respectively], along with lower CRs to steroids [Figure].

**CASE UPDATE**

- The patient received prednisone at a dose of 2 mg/kg daily for 14 days.
- His skin rash was reduced to grade 1 and diarrhea resolved.
- Steroid dose was tapered by 10% every 5 to 7 days.

**How do you define steroid-refractory aGVHD?**

[The definition that] I use was used in the REACH2 study [NCT02913261] of ruxolitinib [Jakafi]. I thought that this was probably the best definition, encompassing everything that I’ve worked with or thought about throughout the years.

According to this definition, steroid-refractory aGVHD includes GVHD that has either increased in stage in any organ system or demonstrated new organ involvement, after 3 days of primary treatment with methylprednisolone [Medrol] at a dose of at least 2 mg/kg daily.3 This part of the definition is something that I initiated a long time ago in my first infliximab [Remicade] study, where I noticed [that those who] progress are not the same as [patients who do not] respond and keep their stage.

[The definition of steroid-refractory aGVHD also includes] GVHD that has not improved, such as if it has not decreased in stage in at least 1 involved organ system, after 7 days of treatment with methylprednisolone at a dose of at least 2 mg/kg daily. Additionally, patients who previously began corticosteroid therapy at a lower dose, at least at 1 mg/kg daily, for treatment of skin GVHD or skin GVHD accompanied by upper GI GVHD, but who develop new GVHD in another organ system, were also included.3

This third category represents something that shouldn’t have happened. Why does a person who has both skin and GI GVHD start with 1 mg/kg per day? If such a patient had been treated adequately, with 2 mg/kg, you might not have been confronted with the situation of steroid refractoriness, which has a mortality [rate] of up to 80%.4

The final category [of steroid-refractory aGVHD] is [represented by] patients who cannot tolerate corticosteroid taper; that is, they begin corticosteroids at 2 mg/kg, demonstrate a response, and progress before a 50% decrease from the initial starting dose of corticosteroids is achieved.3 Some people [call this] steroid dependence, but to me it’s semantic.

I do not [regard] 7 days of 4 L of diarrhea [per day] as the same as 7 days of rash that covers 60% of the BSA. When GVHD is visceral, my tolerance for stability may not be 7 days. That’s 1 thing that I add between parentheses. So,
if you’re confronted with that in practice, you probably want to do something before you reach day 7.

**What does the National Comprehensive Cancer Network (NCCN) recommend for the treatment of patients with steroid-refractory aGVHD?**

There is a long list of NCCN recommendations for the treatment of aGVHD. The reason [for the long list] is that the NCCN is used by payers to decide whether or not they cover [one of the listed treatments for a treatment in the] second line. The intention [in creating the long list] is to make everyone’s life easier. So, when [anyone goes to] look at these guidelines, they should take the time to read the text, because that’s where the [substance] is. According to the guidelines, ruxolitinib, approved for steroid-refractory aGVHD, is the best second-line therapy.

**Upon what data was the approval of ruxolitinib based?**

[Those data came from the] phase 2 REACH1 study [NCT02953678] of ruxolitinib for steroid-refractory patients with aGVHD. The eligibility criteria were, basically, [the same as the] definition of steroid-refractory aGVHD, [as I previously mentioned]. The primary end point was overall response rate [ORR] on day 28, and there were [several] secondary end points. Seventy-one patients were treated [with 5 mg of oral ruxolitinib] twice a day. [Patients also received] steroids, with or without a calcineurin inhibitor, while ruxolitinib acts through the inhibition of STAT1 [and] STAT3, and both are broadly immunomodulatory.3

In the REACH1 study, the ORR on day 28 was 54.9%, and the best ORR [at any time during treatment] was 73.2% with the rates of CR [at 26.8% at day 28; 56.3% at any time during treatment] were considerable for steroid-refractory aGVHD. The median time to response was 7 days [range, 6-49]; the median duration of response was 345 days. The nonrelapse mortality [rate] at 6 months was [44.4%].7 That is quite good, [considering] that 15 to 20 years ago we used to have mortality [rates] of up to 80% at 6 months, while on the trial the median overall survival [OS] for people who responded on day 28 was not reached.

**What were the results of the phase 3 trial of ruxolitinib?**

REACH2 [NCT02913261] was the phase 3 [trial of ruxolitinib] for aGVHD. [In this trial], the dose was 10 mg oral twice a day, and [the experimental therapy] was compared with the best available therapy, selected by the investigator prior to randomization. The primary end point was, again, ORR on day 28, and there was long-term follow-up until month 24.3 The ORR on day 28 was 62.3% for ruxolitinib and 39.4% for the control group [odds ratio, 2.64; 95% CI, 1.65-4.22; \(P<.001\)]. [There was] a nice CR rate, significantly higher for the ruxolitinib arm at 34.4% [vs the control arm at 19.4%]. The durable overall response rate at day 56 was, again, significantly higher in the ruxolitinib arm than in the control arm [at 39.6% vs 21.9%, respectively (odds ratio, 2.38; 95% CI, 1.43-3.94; \(P<.001\))], and this was particularly notable in CRs at [26.6% vs 16.1%, respectively].3 The responses on day 28 [were analyzed for subgroups defined by] stage at randomization. [Patients who started] with a lower grade tended to have better responses. [There was] a CR rate of [50.9%] for grade 2 patients, [28.2% for grade 3], and [20.0%] for grade 4. [The same pattern was observed in the control arm] but with mostly lower values for both CRs and partial responses. Additionally, there was a dramatic difference between the ruxolitinib and control arms with respect to response duration.

The failure-free survival for ruxolitinib at 6 months was about 50%, which is good, because the best available therapy was less than 40%. The adverse events [included] cytopenias, particularly thrombocytopenia at 33% in the experimental arm vs 18% in the control arm, and anemia at 30% vs 28%, respectively. Also, cytomegalovirus infections were notable, but this was not dramatically different between groups [at 26% vs 21%, respectively]. The thrombocytopenia, though, was [dramatically different between groups].8 ■

**REFERENCES**

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.

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Roundtable Discussion: Barriers to CAR T-Cell Therapy for DLBCL Lead to Debate About Targeted Therapy

CASE SUMMARY

A 79-year-old man presented with fever, 7-lb unintentional weight loss and occasional chest pain. He had a history of hypertension controlled with medication. He appeared tired and had palpable bilateral cervical lymphadenopathy. He was negative for hepatitis B, hepatitis C, and HIV.

Laboratory Results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydrogenase</td>
<td>300 U/L (280 U/L upper limit)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.8 g/dL (13 g/dL lower limit)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.3 mg/dL (1.2 mg/dL upper limit)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.7 mg/dL (1.2 mg/dL upper limit)</td>
</tr>
</tbody>
</table>

A lymph node biopsy was performed. Immunohistochemistry panel showed that the patient had diffuse large B-cell lymphoma (DLBCL) with germinal center B-cell (GCB) subtype. He was CD10 and CD20 +. Fluorescence in situ hybridization assay was negative for rearrangements of BCL6, BCL2, and C-MYC.

A whole-body PET/CT scan showed activity in the colonic wall, with the largest node measuring 3.9 cm and with evidence of subcutaneous tissue involvement. An MRI of the brain showed no evidence of lesions. He received a diagnosis of stage IV DLBCL and high-risk disease on the International Prognostic Index. His ECOG performance status was 1.

The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone), which was well tolerated. A PET/CT scan at end of treatment showed a complete response, but 1 year later the patient presented with diffuse lymphadenopathy, confirmed by the PET CT scan. A biopsy showed relapse of the same DLBCL, and the patient was considered ineligible for stem cell transplant. He completed second-line gemcitabine/oxaliplatin (GemOx) plus rituximab, with a partial response. Five months later, he returned with overt disease progression.

DISCUSSION QUESTION

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

**KALAVAR:** I consider the age of the patient, comorbidities, if they are candidates for transplant or CAR [chimeric antigen receptor] T-cell therapy, prior regimen given, and patient choice. If I must send the patient for CAR T-cell therapy, I consider the logistics and availability. Most likely a 79-year-old patient is not a candidate for transplant. I would consider CAR T-cell therapy for this patient, [depending on how] willing he is to travel to a different center for it. These are all the things [I think about] before I make the final decision. 

---

**Pallawi Torka, MD**
(Moderator)
Assistant Professor of Oncology
Lymphoma Section, Department of Medicine
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Buffalo, NY

**PARTICIPANT LIST**
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Raman Sood, MD
Francisco Hernandez-Illizaliturri, MD
Joshua A. Strauss, MD
Rakesh K. Mehta, MD
Varun Modi, MD
Qun Dai, MD

**Event region:** New York/New Jersey
Of course, [I think about] insurance coverage too. But my last patient had no problems having the insurance cover it. There is a delay between securing the CAR T-cell therapy [and receiving treatment], depending on how sick the patient is and how urgent the treatment is.

STEINBERG: This seems like a patient who, if you can get [them] referred for CAR T-cell therapy at this age, could tolerate it. That would be the best approach or best chance for long-term remission. But for whatever reason—if they are too far away, it’s not logistically going to work for them, or if they have poor social support—I’d probably consider polatuzumab vedotin [Polivy].

TORKA: Do you, in the relapsed/refractory setting, think about how cell of origin could be leveraged in terms of therapy? Is that a consideration at all?

STEINBERG: For me, it helps more with prognosis when I talk to the patient, worry about them, or watch them more carefully. But I don’t know if it’s necessarily going to affect my management unless I was trying something off-label, such as abivertinib [Fujovee], maybe, in germinal center B-cell (GCB) lymphoma.

TORKA: Dr Sood, are there any differences in your practice because it’s more in western New York compared with many of our guests who are from closer to [New York City]?

SOOD: My enthusiasm for CAR T-cell therapy has waned over the years [because] the data show it doesn’t seem to be as promising as just chemotherapy. Also, there is the factor of getting the patient back and forth.

I think my preference would be the tafasitamab [Monjuvi] plus lenalidomide [Revlimid] combination….I can deliver it in the community setting, and it seems tolerable. For a 79-year-old patient, I think the outcomes are similar. I would choose [tafasitamab/lenalidomide] for this patient.

TORKA: I want to challenge you on that a little bit. I agree that a majority of the patients do share the same eligibility criteria. However, patients on CAR T-cell therapy studies were even enrolled up to the age of 86, and they could have more organ function compromise compared with those who go into transplant.

With CAR T-cell therapy, patients with active disease can get it. So if they have organ compromise because of active disease, it’s acceptable. But most patients who go to transplant, go in with complete remission [CR], so it is more during consolidation. Although most patients do share the same criteria, which makes them ineligible.

Patients [I’ve seen] who have aggressive disease never make it to CAR T-cell therapy because we don’t have the time. We keep going from treatment to treatment and are never able to get the disease controlled enough to do the CAR T-cell therapy. Has anybody had similar experiences?

STRAUSS: I’ve had experience with patients who get so sick and their relapsing goes fast, while they’re inpatient, and you aren’t going to ship them off from inpatient to CAR T-cell therapy. One gives something a little bit more urgent, something that you can get right away.

TORKA: Now with all these approvals, it is possible that many of the patients get an idea of what can be done in the second or third line [at the academic centers], then the treatment is delivered back in your office.

Is that what has been happening in many cases? Does the academic center suggest treatment and the patients...
come back, or do they just stay at the academic center? Any comments on that from community oncologists?

STRAUSS: It’s mixed. Sometimes they are enamored by the academic institution and decide to stay there. On the flip side, sometimes they go there, and they’d rather go down the street to a smaller practice where you park, you take 2 steps, and you are in the waiting room. Both have a different vibe, and some patients prefer one, and some patients prefer the other. I’d say it’s half-and-half. But if it’s something that I can give in the community setting, I give it.

**POLLING QUESTION**

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

- Polatuzumab vedotin ± bendamustine/rituximab 40% (4)
- Tafasitamab + lenalidomide 40% (4)
- Loncastuximab tesirine 20% (2)
- Rituximab-based chemotherapy 0% (0)
- Other/clinical trial 0% (0)

Total votes: 10

SOOD: What is the response rate of single-agent polatuzumab? What is the benefit of adding BR [bendamustine/rituximab] to it to begin with?

TORKA: Single-agent polatuzumab is not very active. I would say in the initial studies it had overall response rates [ORRs] of [approximately] 20% combined in all lymphomas. Every lymphoma was a small single-digit number. If you are asking for DLBCL, specifically, I don’t know. I tried to look for studies where polatuzumab plus rituximab was given, but there is not much data for that. Although, in clinical practice, it is potent. If I have an older patient who I don’t want to give bendamustine, I start out with polatuzumab plus rituximab for 1 cycle to see how they do, and then add the bendamustine once they feel a little bit better. It works.

HERNANDEZ-ILIZALITURRI: That’s a valid point, especially because lenalidomide alone does not have an FDA level approval for DLBCL. On the other hand, if you look at its long-term data from the L-MIND study [NCT02399085] of tafasitamab/lenalidomide, the patients who respond tend to sustain remission for a long time—more than 4 years. The number of patients who are in that bracket is much higher than those on loncastuximab or pola-BR. So if you find the correct patient, I think it is worth the extra paperwork.

**DISCUSSION QUESTIONS**

- Have you used tafasitamab plus lenalidomide?
- What do you think of the tafasitamab and lenalidomide data?

STEINBERG: The main thing that has limited my use of it is getting lenalidomide. It’s such a hassle because of the co-pay and all the other stuff you go through. I’ve used it, but it’s almost like I use single-agent tafasitamab while waiting for lenalidomide to arrive, and it takes forever, so it increases my dissatisfaction with using it. That’s why, for example, I prefer the treatments that are IV [intravenous] that you can give every couple of weeks, such as polatuzumab or loncastuximab.

HERNANDEZ-ILIZALITURRI: That’s a valid point, especially because lenalidomide alone does not have an FDA level approval for DLBCL. On the other hand, if you look at its long-term data from the L-MIND study [NCT02399085] of tafasitamab/lenalidomide, the patients who respond tend to sustain remission for a long time—more than 4 years. The number of patients who are in that bracket is much higher than those on loncastuximab or pola-BR. So if you find the correct patient, I think it is worth the extra paperwork.

TORKA: Both points are valid. At academic cancer centers, we are spoiled because we have whole teams that are working on the prior authorizations and such. What about the other community practices? Is [difficulty] getting lenalidomide approval something that is commonly experienced in the community?

SOOD: For me, it’s not good in the community setting. But, in general, it’s not a huge barrier. If you believe in it, I think you can get it done.

STEINBERG: In general, getting the oral drugs is more difficult because they require co-pay assistance, and you must go through the REMS [Risk Evaluation and Mitigation Strategy] program for lenalidomide, which is a little bit of a different process than for something we give IV. When it is something IV, the hospital runs our infusion center, so we just order it, and that’s all done on the back end, and it’s not something that we as a practice worry about. The oral drugs are a little trickier and can potentially be more costly to the patient.

TORKA: Dr Mehta, do you have pharmacists to help you with the REMS program and such, or is it all falling on the practitioner?
MEHTA: Yes, we have pharmacies, but most of the responsibility is on the physicians. We take care of that, but they help us in preparing the chemotherapy and immunotherapy.

TORKA: So all the paperwork falls on you to do in the clinic?

MEHTA: Most often, yes.

SOOD: REMS is done by the nurses. I have not done REMS myself. I have a nurse who is designated to do that, and she does more than that. It is not that big a hassle once you have it streamlined. We do it for my patients all the time; almost every one of my patients is on lenalidomide.

MODI: We do not have a pharmacist but have staff who work on this paperwork for us.

TORKA: Tafasitamab is an anti-CD19 monoclonal antibody that is FC-enhanced. It is a little bit genetically engineered, but it works like any other monoclonal antibody. [What are your thoughts on the data for tafasitamab plus lenalidomide?]

HERNANDEZ-ILIZALITURRI: When you look at the response rate of the patients based on cell of origin, the non–GCB DLBCL response was [approximately] 70%, which is much higher. Unfortunately, that was not the primary end point of the study, so it doesn’t get highlighted in the manuscript a lot.1 This is something to take notice of, especially when you are trying to identify the patients who most likely will respond to this regimen.

The other thing is looking at the dosing of lenalidomide....I think it’s very important to try to give as much as the patient can tolerate, in contrast to multiple myeloma or chronic lymphocytic leukemia, low-dose lenalidomide barely has activity in DLBCL. I try not to go below 15 mg because I think you will lose activity in this kind of patient.

TORKA: These are good points. For the GCB and non–GCB points, which Dr Hernandez is alluding to, rituximab and lenalidomide had good activity in activated B-cell [aBC] DLBCL but it had barely any activity in GCB DLBCL; however, tafasitamab plus lenalidomide has blanket approval. In the manuscript, they don’t have the breakdown of GCB or non–GCB outcomes. So we reached out to the company to ask. The company shared the data showing that patients who have non–GCB or aBC DLBCL, because it is driven by the NF-κB pathway, respond better to lenalidomide, and the responses of tafasitamab plus lenalidomide are better in those patients.

In my practice, if I must choose between pola-BR and tafasitamab plus lenalidomide at that point. I don’t think these data are published anywhere, but the response rates with tafasitamab plus lenalidomide are rather low in patients with GCB DLBCL. I would say they are probably 25% to 30%. In that case, it’s fair game whether you want to use tafasitamab plus lenalidomide or pola-BR.

SOOD: Does cell of origin evolve from one cell to another? After the initial biopsy, do you need to rebiopsy these patients?

HERNANDEZ-ILIZALITURRI: Normally the [cell of origin] doesn’t change the cell of origin. If they had GCB to begin with, they will have GCB to the end.

SOOD: There is no change of phenotype?

TORKA: We do recommend biopsy with each line of therapy because we want to confirm the diagnosis. Sometimes it’s obvious, but sometimes it’s not. It is important to test for that. If it is an older patient, I try to do bone marrow biopsies just to see what the bone marrow reserve is and what might be tolerated better for these patients. Both regimens are pretty myelosuppressive.

DISCUSSION QUESTION

What do you think of loncastuximab tesirine for this patient population?

TORKA: Loncastuximab is less myelosuppressive, so that might be a consideration. It was just approved recently, so there is no familiarity with it. Is there any concern that you have with loncastuximab, or is it that it’s new, you are not familiar with it, and we don’t know what the niche might be?

STEINBERG: I have given it to 1 patient who had received polatuzumab in the past; they were inpatient, a little bit debilitated, and it would have taken a long time because we don’t have inpatient formulary for lenalidomide. We decided to use [loncastuximab]. When I shared the data with the patient and family, it sounded good: 48% ORR.2 The median time to response was [approximately] 2 months. It was quite an aggressive lymphoma. Overall, it seemed like a reasonable option short of doing palliative care at that point. So they were willing to try.

TORKA: Kudos that you were able to get it in the inpatient setting. That must have required a lot of convincing.

SOOD: We have an amazing pharmacist, and if the data are there, we can use it inpatient.
TORKA: I don’t think I can use it here at Roswell Park. They will not let me. But you bring up a good point…if you see time to first response, all the [later-line DLBCL] studies will tell you 2 months. That is because the first scan will be done in 2 months. So that is the official time to first response, but the clinical response is much faster.

HERNANDEZ-ILIZALITURRI: By the time they are getting third-line therapy…chances are they responded to treatment.

DAI: I think loncastuximab is an option for [older patients] who cannot tolerate aggressive treatments such as CAR T-cell therapy. The schedule is good; you do it once every 3 weeks and keep going. I would certainly choose it for the patient who is not a candidate for CAR T-cell therapy or transplant. There is concern that after you use it, it may knock off the CD19 and reduce the efficacy of future CAR T-cell therapy, even though the data show 15 patients who had this treatment and proceeded with CAR T-cell treatment and showed response [Table 2,3]. I feel it is a treatment option for us in a select group of patients.

SOOD: I have not had a chance to use it yet. It seems tolerable and easier.

HERNANDEZ-ILIZALITURRI: We have used it at our institute. I think on the positive side it is very easy to administer. It is very well tolerated and some patients respond. Sometimes you can palliate them and give them a couple of more months with their families. But the duration of the response is short.

I think this is a good drug if you have a patient you want to get through the holidays without him or her being admitted to the hospital, trying to make the family happy, or trying to get them to some event. But it is not something that is going to give you long mileage. I think an important point you talked about is checking for CD19 expression prior to CAR T-cell therapy if a patient is to receive CD19-directed therapy. This is a situation in which a fresh biopsy is important because there is no accurate CD19 antibody test, so you rely on flow cytometry, and for that you need fresh, living cells. I think that is very important when you advise these patients and talk to the pathologist and tell them what you are looking for, because you are going to depend on flow cytometry for that.

TORKA: Dr Steinberg, you mentioned that you used it in an inpatient? What happened to that patient?

STEINBERG: The patient ended up passing away, just progression of disease.

TORKA: Did they get any benefit, even for a few weeks?

STEINBERG: Yes, initially the lactate dehydrogenase did decrease as a marker for response, but it was such a kinetically aggressive lymphoma and this was a last hurrah. Aside from palliative care, we decided to give it a try. I could see a role for it, maybe in less aggressive lymphomas, not those with say a Ki67 of 90%, but in DLBCL maybe with 60%, so not as aggressive. It’s just anecdotal, from my experience with 1 patient.

TORKA: None of us have used it all that much, so we must learn from each other’s experience.

DISCUSSION QUESTION

When you think about each of these newer therapies, what patient comes to mind as a perfect fit?

MODI: It depends on the patient’s comorbidities, performance data, and the prior response. Let’s say the patient has bad neuropathy; polatuzumab wouldn’t be a great option, so we could use tafasitamab plus lenalidomide or loncastuximab.

TORKA: Absolutely. Comorbidities are something that must be considered. Lenalidomide is an older drug, which sometimes is a big problem because you have other options, so why spend so much time trying to get it.

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

TABLE. Loncastuximab Tesirine Response After CAR T-Cell Therapy2,3

| Best response to CAR T-cell therapy, n (%) | CR | 7 (54) |
| Best response to loncastuximab post CAR T-cell therapya, n (%) | CR | 2 (15.4) |
| | PR | 4 (30.8) |
| | SD | 1 (7.7) |
| | PD | 2 (15.4) |

CAR, chimeric antigen receptor; CR, complete response, PD, progressive disease; PR, partial response; SD, stable disease

afour patients not evaluable (30.8%).
LIBTAYO is indicated for the first-line treatment of patients with non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is:

- Locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- Metastatic

NCCN Guidelines® for Non–Small Cell Lung Cancer recommend cemiplimab-rwlc (LIBTAYO) as a Category 1* (preferred) systemic therapy option for advanced NSCLC†

Approved in patients with advanced NSCLC* with PD-L1 ≥50% and no EGFR, ALK, or ROS1 aberrations‡

LIBTAYO significantly EXTENDED SURVIVAL vs platinum-based chemotherapy in EMPower-Lung 1,3

Study design

**EMPOWER-Lung 1** was a large, phase 3, randomized, open-label, multicenter study that included patients with locally advanced NSCLC who were not candidates for treatment with definitive concurrent chemoradiation or patients with stage IV disease who received no prior systemic treatment for recurrent or metastatic NSCLC. Key eligibility criteria included PD-L1 expression ≥50% and ECOG PS 0 or 1. Patients with type 1 diabetes mellitus or hypothyroidism only requiring hormone replacement were eligible. Patients with brain metastases that were treated and clinically stable (neurologically returned to baseline) for at least 2 weeks prior to randomization were permitted. Radiological confirmation of stability or response was not required. Patients were excluded if they had EGFR, ALK, or ROS1 aberrations, a medical condition that required systemic immunosuppression, uncontrolled infections with hepatitis B, hepatitis C, or HIV, autoimmune disease that required systemic therapy within 2 years of treatment, and never-smokers.1,4

Patients were randomized 1:1 to receive LIBTAYO 350 mg IV Q3W for up to 108 weeks or investigator’s choice of the following platinum-doublet chemotherapy regimens for 4 to 6 cycles: paclitaxel + cisplatin or carboplatin; gemcitabine + cisplatin or carboplatin; or pemetrexed + cisplatin or carboplatin followed by optional pemtrexed maintenance in patients with nonsquamous histology. Treatment with LIBTAYO continued until RECIST 1.1-defined progressive disease on therapy with LIBTAYO were permitted to continue treatment with LIBTAYO 350 mg Q3W for up to 108 additional weeks, along with the addition of histology-specific chemotherapy for 4 cycles until further progression was observed. Patients who experienced IRC-assessed RECIST 1.1-defined progressive disease on chemotherapy were permitted to receive treatment with LIBTAYO monotherapy until further progression, unacceptable toxicity, or for up to 108 weeks.1,3

The primary efficacy endpoints were OS and PFS. Secondary endpoints included ORR (key), DOR, and safety and tolerability.1,4

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.1

**Important Safety Information**

**Warnings and Precautions**

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
In an analysis of the subset of patients with advanced NSCLC who had no EGFR, ALK, or ROS1 aberrations and known PD-L1 ≥50% (n=563):

Overall survival with LIBTAYO vs platinum-based chemotherapy in EMPOWER-Lung 13-5

![Probability of OS](image)

- Number of deaths: 25% of patients (70 out of 283 patients) with LIBTAYO and 38% of patients (105 out of 280 patients) with chemotherapy4,5
- 72% of patients who progressed on platinum-based chemotherapy crossed over to LIBTAYO treatment6

**Clinical safety data**

- LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients;
- Adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke, and increased aspartate aminotransferase
- Serious adverse reactions occurred in 28% of patients receiving LIBTAYO;
- The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis

**Important Safety Information (continued)**

**Warnings and Precautions (continued)**

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Early identification and management are essential to ensuring safe use of PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions includes the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor 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.

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

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 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 corticosteroids.

**Immune-mediated pneumonitis:** LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

Warnings and Precautions (continued)

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld or permanently discontinued, 6% (1/18) of patients had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or if total bilirubin increases to more than 3 times the ULN. For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids; of these, none had recurrence within 12 weeks of initiating steroids.

Immune-mediated endocrinopathies: For Grade 3 or 4 endocrinopathies, withhold until clinically stable or permanently discontinue depending on severity.

• Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67.5% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

• Hypophysitis: LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

• Thyroid disorders: LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity.

• Thyroiditis: Thyroiditis occurred in 0.5% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

• Hypothyroidism: Hypothyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hypothyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hypothyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hypothyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

• Hyperthyroidism: Hyperthyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hyperthyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hyperthyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hyperthyroidism, 1 reinitiated LIBTAYO after symptom improvement, 1 required ongoing hormone replacement therapy.

• Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of
**Important Safety Information (continued)**

**Warnings and Precautions (continued)**

**Severe and Fatal Immune-Mediated Adverse Reactions (continued)**

**Immune-mediated dermatologic adverse reactions (continued):** the
11 patients in whom LIBTAYO was withheld for dermatologic adverse
reactions, reinitiated LIBTAYO after symptom improvement; of these,
43% (3/7) had recurrence of the dermatologic adverse reaction. Topical
emollients and/or topical corticosteroids may be adequate to treat mild to
moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS,
TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS,
TEN, or DRESS. Resume in patients with complete or partial resolution (Grade
0 to 1) after corticosteroid taper. Permanently discontinue if no complete
or partial resolution within 12 weeks of initiating steroids or inability to
reduce prednisone to less than 10 mg per day (or equivalent) within
12 weeks of initiating steroids.

**Other immune-mediated adverse reactions:** The following clinically
significant immune-mediated adverse reactions occurred at an incidence of
<1% in 810 patients who received LIBTAYO or were reported with the use of
other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been
reported for some of these adverse reactions.

- **Cardiac/vascular:** Myocarditis, pericarditis, and vasculitis. Permanently
discontinue for Grades 2, 3, or 4 myocarditis.
- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination,
  myasthenic syndrome/myasthenia gravis (including exacerbation),
  Guillain–Barré syndrome, nerve paresis, and autoimmune neuromyopathy.
  Withhold for Grade 2 neurological toxicities and permanently discontinue
  for Grades 3 or 4 neurological toxicities. Resume in patients with complete
  or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently
  discontinue if no complete or partial resolution within 12 weeks of
  initiating steroids or inability to reduce prednisone to less than 10 mg per
day (or equivalent) within 12 weeks of initiating steroids.
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. 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
  Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with
  systemic steroids to reduce the risk of permanent vision loss.
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and
  lipase levels, gastritis, duodenitis, stomatitis.
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.
- **Endocrine:** Hypoparathyroidism.
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia.
  Hemophagocytic lymphohistiocytosis, systemic inflammatory
  response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi
  lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid
  organ transplant rejection.

**Infusion-related reactions**

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients
receiving LIBTAYO as a single agent. Monitor patients for signs and
symptoms of infusion-related reactions. The most common symptoms of
infusion-related reaction were nausea, pyrexia, rash, and dyspnea. Interrupt
or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for
Grade 3 or 4.

**Complications of allogeneic HSCT**

Fetal 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/PD-L1–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/PD-L1 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/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

**Embryo-fetal toxicity**

LIBTAYO can cause fetal harm when administered to a pregnant woman due
to an increased risk of immune-mediated rejection of the developing fetus
resulting in fetal death. Advise women of the potential risk to a fetus. Advise
females of reproductive potential to use effective contraception during
treatment with LIBTAYO and for at least 4 months after the last dose.

**Adverse Reactions**

- In the pooled safety analysis of 810 patients, the most common adverse
  reactions (≥15%) with LIBTAYO were musculoskeletal pain, fatigue, rash,
  and diarrhea.

- In the pooled safety analysis of 810 patients, the most common
  Grade 3–4 laboratory abnormalities (≥2%) with LIBTAYO were:
    - lymphopenia, hyponatremia, hypophosphatemia, increased aspartate
      aminotransferase, anemia, and hyperkalemia

**Use in Specific Populations**

- **Lactation:** Because of the potential for serious adverse reactions in
  breastfed children, advise women not to breastfeed during treatment and
  for at least 4 months after the last dose of LIBTAYO.

- **Females and males of reproductive potential:** Verify pregnancy status in
  females of reproductive potential prior to initiating LIBTAYO.

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

**References:**

1. LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing
   information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.
2. Referenced with permission from the NCCN Clinical Practice Guidelines
   © National Comprehensive Cancer Network, Inc. 2021. All rights reserved.
   Accessed June 16, 2021. To view the most recent and complete version of the
   Cemiplimab monotherapy for first-line treatment of advanced non-small-cell
   lung cancer with PD-L1 ≥ of at least 50%: a multicentre, open-label, global,
   treatment of advanced non-small-cell lung cancer with PD-L1 of at least
   50%: a multicentre, open-label, global, phase 3, randomised, controlled
   trial. Lancet. 2021;397(10274):592-604. 5. PD-L1 IHC 22C3 pharmDx
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Immune-Mediated Pneumonitis

require systemic steroids (e.g., endocrinopathies and dermatologic reactions) corticosteroids. whose immune-mediated adverse reactions are not controlled with until improvement to Grade 1 or less. Upon improvement to Grade 1 or immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. 

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor 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 LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 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 corticosteroids.

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

LIBTAYO can cause immune-mediated pneumonitis. The definition of immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.4% of patients and withholding of LIBTAYO in 2.1% of the patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld for pneumonitis, 9 restarted LIBTAYO after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis.

Immune-Mediated Colitis

LIBTAYO can cause immune-mediated colitis. The definition of immune-mediated colitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. The primary component of the immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%) adverse reactions. Colitis led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld for colitis, 4 restarted LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence of colitis. Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immune-mediated hepatitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Nineteen percent (19%) of these patients (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients restarted LIBTAYO after symptom improvement; of these, none had recurrence of hepatitis. Immune-Mediated Endocrinopathies

Adrenal Insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff. Hypophysitis

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypothalamic-pituitary dysfunction. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff. Thyroid Disorders

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hypothyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Thyroiditis: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.
Hyperthyroidism: Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthermia resolved in 50% of the 26 patients.

Of the 12 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reintiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hypothyroidism: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reintiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

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 LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-Mediated Nephritis with Renal Dysfunction

LIBTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Immune-mediated nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for nephritis, 2 reintiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reintiated LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve oaresis, autoimmune neuromyasthenia

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. 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 to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea.

Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.3) in the full prescribing information].

5.3 Complications of Allogeneic HSCT

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/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic vaso-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/PD-L1 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/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6. ADVERSE REACTIONS

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

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for ≥ 6 months and 25% were exposed for ≥ 12 months. In this pooled safety population, the most common adverse reactions (≥15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.
Non-Small Cell Lung Cancer (NSCLC)

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Studies (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22 % were exposed for ≥ 12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 6 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

Table 6: Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3-4 %</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.7</td>
<td>16</td>
</tr>
<tr>
<td>Electrolytes</td>
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<td></td>
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<tr>
<td>Hyponatremia</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>4.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2.4</td>
<td>4.1</td>
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<td>Hypermagnesemia</td>
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<td>1.6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypercalciemia</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

As with all therapeutic proteins, there is a 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 to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death [see Data]. Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the
blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation
Risk Summary
There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO [see Use in Specific Populations (8.1)].

Contraception
LIBTAYO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Females
Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

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

8.5 Geriatric Use
Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 219 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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LIB.21.03.0027  03/21
Antonarakis Reviews Clinical Trials of Cabazitaxel and 177Lu-PSMA-617 for mCRPC

**CASE**

- A 75-year-old man presented with intermittent right hip pain.
- Physical exam: unremarkable
- Clinical work-up:
  - Prostate-specific antigen (PSA): 32.6 ng/mL
  - Bone scan and abdominal/pelvic CT scan: negative
  - Transrectal ultrasonography biopsy
    Gleason 4 + 4, grade group 4
  - Negative bone scan and abdominal/pelvic CT scan
  - Stage T2N0M0
  - ECOG performance status: 1
- Treatment and follow-up:
  - External beam radiation therapy plus androgen deprivation therapy (ADT) was initiated, planned for 18 months.
  - Undetectable PSA level at 6-month follow-up; testosterone at castrate level; asymptomatic
- Six months later, the patient developed new hip pain and urinary frequency.
  - PSA: 29.4 ng/mL
  - Testosterone: 10 ng/dL
- Bone scan showed evidence of 2 osteoblastic lesions in the right hip (0.8 cm and 1.1 cm).
- Abdominal/pelvic CT showed a 2.1-cm left pelvic lymphadenopathy.
- He is now considered metastatic and castration resistant.
- The patient started treatment on enzalutamide (Xtandi) 160 mg by mouth daily.
- PSA decreased to nadir of 3.9 ng/mL 4 months after starting enzalutamide.
- After 8 months on enzalutamide, the patient had a PSA level of 60.7 ng/mL.
- Abdominal/pelvic CT showed enlargement of known pelvic lymph nodes.
  - Bone scan showed progressive disease.
  - The patient started on docetaxel 75 mg/m² intravenously every 3 weeks and daily prednisone 5 mg by mouth every 12 hours.
  - After 6 cycles, he developed bilateral digital neuropathy and docetaxel was held.
  - After 3 months, he had a rising PSA level and back pain.
  - Imaging: enlargement of known pelvic lymph nodes and 1 new liver lesion.

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Division of Hematology, Oncology and Transplantation
Associate Director of Translational Research
Masonic Cancer Center
University of Minnesota
Minneapolis, MN

**Targeted Oncology™: What do the National Comprehensive Cancer Network (NCCN) guidelines advise about the use of cabazitaxel (Jevtana) for metastatic castration-resistant prostate cancer (mCRPC)?**

**ANTONARAKIS:** There are some guidances in the NCCN guidelines. A 20-mg/m² or 25-mg/m² starting dose can be used; both are FDA approved.1 The 25 mg/m² dose has slightly higher objective response rate [ORR], but that did not translate into a longer progression-free survival [PFS] or overall survival [OS].

Then, in certain cases where you have a clinically defined neuroendocrine prostate cancer or aggressive variant prostate cancer, there is a *Lancet Oncology* publication showing that cabazitaxel 20 mg/m² plus carboplatin 4 mg/mL/min was superior in terms of PFS compared with just cabazitaxel.2 So cabazitaxel/carboplatin is [recommended] for these patients who have clinical features suggestive of neuroendocrine prostate cancer like visceral metastasis, low PSA, bulky disease, high lactate dehydrogenase, high carcinoembryonic antigen, synaptophysin, or chromogranin. The 20-mg/m² dose in terms of the myelosuppression, in my opinion, is much better tolerated. I still use growth factor support with the 20-mg/m² dose as well. That is my personal preference, but I think the [risk of] grade 3 and grade 4 neutropenia and thrombocytopenia [is managed] better with the 20-mg/m² dose.
Please discuss the study design and goals of the phase 4 CARD trial (NCT02485691) of cabazitaxel.

This is a pivotal study, which is called a phase 4 trial because it is a postmarketing trial. The CARD trial was done primarily in Europe, and this was for patients who had all received and progressed after 1 androgen receptor [AR]-targeted therapy and docetaxel. It was a third-line mCRPC setting, and this study was done in the days when we were not using either of those agents in the metastatic hormone-sensitive setting. So the vast majority of these patients got both the taxane and the AR-targeting therapy for mCRPC in 1 sequence or the other.

A very important eligibility [requirement] for this trial that many people overlook is that to be eligible, the patients must have previously failed their AR-targeted therapy within less than 12 months, and the reason that this is important is with a first-line AR-targeted therapy for mCRPC, only about one-third of patients progress within 12 months; the median is closer to 18 months. So in a way, this trial was preselecting patients who had a clinical definition of more AR-indifferent disease.

The 2 arms were treatment with the alternative AR therapy or with cabazitaxel at the 25 mg/m² dose every 3 weeks. The primary end point was called imaging-based PFS, but it was basically a radiographic PFS.

There were about 130 patients in the 2 arms. There were roughly an equal number of patients over 75 years although slightly more older patients received cabazitaxel. [In the cabazitaxel arm, 66.7% of] patients had pain at the time of enrollment [vs 71.4% in the control arm]. There were more patients with M1 disease at diagnosis but de novo metastatic disease in the control arm of abiraterone [Zytiga] or enzalutamide.

In terms of the split between abiraterone and enzalutamide and the docetaxel, only [10.9% of patients in the cabazitaxel arm and 14.3% in the control arm] had received 1 of those 2 agents in the metastatic hormone-sensitive setting. Most of those patients received both agents for mCRPC. The median duration of the prior AR therapy was about 8 months in both groups. Remember that to be eligible, these patients had to have an ablation within 12 months. So those 2 estimates do not reflect the real-world median responsiveness to AR-targeted agents because the trial selected the agent for those patients.

What were the results of the CARD trial?

The primary end point was positive favoring cabazitaxel with a pretty robust, almost 50%, relative improvement in progression with an HR of 0.54 [95% CI, 0.40-0.73; \( P < .001 \)], and the median PFS results were quite different: 3.7 months to progression [for the comparator arm] vs 8.0 months to progression [for the cabazitaxel arm].

In every single preplanned subgroup, the [HR for imaging-based progression or death] favored the cabazitaxel arm. Some of the upper limits of the confidence intervals did cross 1.0, but, in my opinion, there was a very consistent trend favoring [cabazitaxel in] all or most subgroups. Interestingly, if you look at

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**FIGURE.** Survival Outcomes in the Phase 4 CARD Trial

![Survival Outcomes in the Phase 4 CARD Trial](image-url)

PFS, progression-free survival; OS, overall survival.
patients with visceral metastases, there was a very clear benefit in those without visceral metastasis [HR, 0.50; 95% CI, 0.36-0.69]. For those with visceral metastases, the cabazitaxel still showed a benefit, but the confidence interval crossed 1.0 and [the upper limit went] all the way up to 1.52 [HR, 0.79; 95% CI, 0.41-1.52]. But my interpretation of this is that there was a consistent benefit. The benefit did not seem to be restricted to just 1 or 2 different scenarios.

Composite PFS included both radiographic or symptomatic progression [or death]. So if a patient had a progressive bone pain even in the absence of radiographic progression, that would count. This did not include [an increase in] PSA in the definition of progression, and there was a big difference with a HR of 0.52 [95% CI, 0.40-0.68; P < .0001].

The part that surprised everybody, including myself, and the aspect that made this trial so practice-changing, in my opinion, was that the OS was also numerically and statistically different and different in a clinically meaningful way with a decreased rate of death of about 36%. The HR was 0.64 [95% CI, 0.46-0.89; P = .008 (Figure 3)]. Every secondary end point also favored the cabazitaxel group: PSA response, objective tumor response, and pain response, as well as an improvement in the time to first skeletal symptomatic event.

What was the safety and tolerability observed in this trial?

The adverse events [AEs] were numerically greater in the cabazitaxel arm, with about 20% of patients having to discontinue cabazitaxel because of AEs, whereas only 9% of patients who received abiraterone or enzalutamide had to discontinue because of AEs. Despite the slight increase in AEs, the quality of life on the FACT-P [Functional Assessment of Cancer Therapy–Prostate] scale, cabazitaxel did better than abiraterone and enzalutamide whether you are talking about physical well-being, social well-being, emotional well-being, or functional well-being.

[Looking at the] trends across time, on the prostate-specific well-being scale, it did not reach significance but the patients who received cabazitaxel are consistently above those who received abiraterone or enzalutamide, especially for the first 6 to 9 months, and then their pain-related [well-being] was superior and also statistically significant, meaning that cabazitaxel was more effective by controlling pain and preventing pain progression.

Please discuss the background of the phase 3 VISION trial (NCT03511664) of 177Lu-PSMA-617 (Pluvicto).

This is the study that led to the March 23 FDA approval of 177Lu-PSMA-617, which is now called Pluvicto. This was a phase 3 trial. It was a third-line mCRPC study. Patients had to have received at least 1 AR pathway inhibitor and at least 1 or up to 2 taxane regimens, had to have an ECOG performance status of 0 to 2, life expectancy greater than 6 months, and, very importantly, had to undergo a PSMA [prostate-specific membrane antigen] PET scan.

In this trial, it happened to be a 68Gallium-PSMA-11 PET scan. We were all surprised that the FDA specifically called out the 68Gallium-PSMA-11 PET scan as opposed to just any PSMA PET scan, and there are some questions in my mind about...whether it will have to be 68Gallium-PSMA-11, which is not widely available.”

—EMMANUEL S. ANTONARAKIS, MD
dichloride [Xofigo], and sipuleucel-T [Provenge]. Therapies that were permitted were alternative AR-directed agents, steroids, or other palliative maneuvers like palliative radiotherapy, etc. The primary end point was radiographic PFS, with OS being a key secondary end point but not a coprimary end point.

Why were there discrepancies in the patient population of this trial?
This is where it gets a little bit complicated. There were 2 evaluable populations. One was 581 patients, and then the total was 831. There was a difference because when the study was first initiated, a number of sites were enrolling patients who would agree to continue on the study only if they were randomized to lutetium. This was mainly in sites such as Europe, where $^{177}$Lu-PSMA-617 was liberally available outside the trial.

What happened was that in many sites in the first 3 to 6 months of the trial, if a patient in Germany, for example, was randomized to the best-supportive-care arm, they would basically drop out, and after about a quarter of the patients were enrolled, the FDA realized that there was going to be a very large skew in favor of people dropping out of the control arm.

They tightened up the protocol to mandate that patients had to guarantee ahead of time that if they get randomized to the control arm, they will stay on the study, and they basically closed down all the sites where the investigators were encouraging their patients to drop out if they did not get $^{177}$Lu-PSMA-617, which, frankly, was happening.

After that amendment was made to the protocol, they felt that they could reliably evaluate PFS in those patients who subsequently enrolled, which was the remaining 581, but they could also do an OS analysis of the entire intention-to-treat population even after they included those dropouts. It is a slightly complicated explanation but that is why there are 2 populations that were evaluated.

Overall, about 10% of these patients had lung metastases, 12% to 13% had liver metastases, and approximately 40% received cabazitaxel. So, virtually all had received docetaxel but about 40% received cabazitaxel as well. But again, a lot of these were at European sites.

What were the efficacy and safety results of this trial?
There was a very robust improvement in the primary end point of radiographic PFS [HR, 0.40; 99.2% CI, 0.29-0.57; 1-sided $P<.001$], which I think is the most impressive HR for OS that we have seen yet in a mCRPC study but also the absolute difference in median OS going from the median OS of [11.3] months to [15.3] months, which I think is quite impressive.

[Looking at how] the 2 arms compare in terms of AEs, first of all, bone marrow suppression was definitely more prevalent in the $^{177}$Lu-PSMA-617 group. The rate of bone marrow suppression was 47% vs 17% in the control arm. Then in terms of grade 3 to 5 bone marrow suppression, it was 23% vs [about] 7%, which is pretty significant.

PSMA is highly expressed in the parotid, submandibular, and sublingual salivary glands. It is also expressed in the lacrimal glands. So when you give $^{177}$Lu-PSMA-617, you essentially ablate, sometimes permanently, the salivary glands and sometimes the lacrimal glands. So dry mouth and dry eyes are a troublesome AE. Dry mouth occurred in 39% who received $^{177}$Lu-PSMA-617 vs 1% with best supportive care. Oftentimes when this occurs, it does tend to be permanent. There is not that much improvement after the treatment is stopped.

What is the current state of $^{177}$Lu-PSMA-617 treatment for these patients?
The VISION trial led to the FDA approval on March 23, 2022. These patients require a PSMA PET scan. We were all surprised that the FDA specifically called out the $^{68}$Gallium-PSMA-11 PET scan as opposed to just any PSMA PET scan, and there are some questions in my mind about whether any PSMA PET scan will be sufficient or whether it will have to be $^{68}$Gallium-PSMA-11, which is not widely available.
**POLIVY + bendamustine + a rituximab product (BR)**

**Twice the response and double the duration with POLIVY+BR vs BR**

<table>
<thead>
<tr>
<th>Response rates</th>
<th>Duration of response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response rate at EOT</strong></td>
<td><strong>In patients achieving a BOR</strong></td>
</tr>
<tr>
<td>POLIVY+BR</td>
<td>40%</td>
</tr>
<tr>
<td>(n=16/40)</td>
<td>95% CI: 25, 57</td>
</tr>
<tr>
<td>BR</td>
<td>18%</td>
</tr>
<tr>
<td>(n=7/40)</td>
<td>95% CI: 7, 33</td>
</tr>
</tbody>
</table>

63% of patients in the POLIVY+BR arm (n=25/40) achieved a BOR compared to 25% in the BR arm (n=10/40).

In patients achieving a BOR, 64% achieved a DoR ≥ 6 months in the POLIVY+BR arm (n=16/25) compared to 30% in the BR arm (n=3/10).

*EOT was defined as 6 to 8 weeks after Day 1 of cycle 6 or last study treatment. All endpoints were assessed by IRC. BOR was defined as having a CR or PR at any time in the study. DoR was based on BOR.

**Indication**

POLIVY in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least 2 prior therapies.

Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**Important Safety Information**

**Peripheral Neuropathy**

POLIVY can cause peripheral neuropathy, including severe cases. Peripheral neuropathy occurs as early as the first cycle of treatment and is cumulative. POLIVY may exacerbate preexisting peripheral neuropathy.

In Study GO29365, 173 patients treated with POLIVY, 40% reported new or worsening peripheral neuropathy, with a median time to onset of 2.1 months.

Monitor for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of POLIVY.

**Infusion-Related Reactions**

POLIVY can cause infusion-related reactions, including severe cases. Delayed infusion-related reactions as late as 24 hours after receiving POLIVY have occurred. With premedication, 7% of patients (12/173) in Study GO29365 reported infusion-related reactions after administration of POLIVY.

Administer an antihistamine and an antipyretic prior to the administration of POLIVY, and monitor patients closely throughout the infusion. If an infusion-related reaction occurs, slow or interrupt the infusion and institute appropriate medical management.

**Myelosuppression**

Treatment with POLIVY can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In patients treated with POLIVY plus bendamustine and a rituximab product (BR) (n=45), 42% received primary prophylaxis with granulocyte colony-stimulating factor. Cytopenias were the most common reason for treatment discontinuation (18% of all patients).

Monitor complete blood counts throughout treatment. Cytopenias may require a delay, dose reduction, or discontinuation of POLIVY. Consider prophylactic granulocyte colony-stimulating factor administration.

**Serious and Opportunistic Infections**

Fatal and/or serious infections, including opportunistic infections such as sepsis, pneumonia (including *Pneumocystis jiroveci* and other fungal pneumonia), herpesvirus infection, and cytomegalovirus infection have occurred in patients treated with POLIVY. Grade 3 or higher infections occurred in 32% (55/173) of patients treated with POLIVY. Infection-related deaths were reported in 2.9% of patients within 90 days of last treatment.

Closely monitor patients during treatment for signs of infection. Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus.

**Progressive Multifocal Leukoencephalopathy (PML)**

PML has been reported after treatment with POLIVY (0.6%, 1/173). Monitor for new or worsening neurological, cognitive, or behavioral changes. Hold POLIVY and any concomitant chemotherapy if PML is suspected, and permanently discontinue if the diagnosis is confirmed.

**Tumor Lysis Syndrome (TLS)**

POLIVY may cause TLS. Patients with high tumor burden and rapidly proliferating tumors may be at increased risk of TLS. Monitor closely and take appropriate measures, including TLS prophylaxis.
Provide the first CD79b-directed antibody-drug conjugate for R/R DLBCL, NOS, after at least 2 prior therapies\(^1,3\)

**POLIVY** is engineered for targeted activity against dividing B cells\(^1,3\)

**POLIVY** is composed of the potent cytotoxin MMAE and a CD79b-directed monoclonal antibody\(^1\)

**CD79b** is a prime target for DLBCL. It is expressed in >95% of rapidly proliferating B cells, including DLBCL tumor cells\(^2-4\)

**MMAE**=monomethyl auristatin E.

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**Hepatotoxicity**

Serious cases of hepatotoxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with POLIVY.

Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level.

**Embryo-Fetal Toxicity**

Based on the mechanism of action and findings from animal studies, POLIVY can cause fetal harm when administered to a pregnant woman. When administered to rats, the small molecule component of POLIVY, monomethyl auristatin E, caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities, at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with POLIVY and for at least 5 months after the last dose.

**Lactation**

Advise women not to breastfeed during treatment with POLIVY and for at least 2 months after the last dose.

**The Most Common Adverse Reactions**

The most common adverse reactions (≥20%) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

In Study GO29365, fatal adverse reactions occurred in 7% of recipients of POLIVY plus bendamustine and a rituximab product (BR) (n=45) within 90 days of last treatment. Serious adverse reactions occurred in 64% of patients, most often from infection. Serious adverse reactions occurring in ≥5% of recipients of POLIVY plus BR included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%).

Safety was also evaluated in 173 adult patients with relapsed or refractory lymphoma who received POLIVY, bendamustine, and either a rituximab product or obinutuzumab in Study GO29365, including the 45 patients with DLBCL. Fatal adverse reactions occurred in 4.6% of recipients of POLIVY within 90 days of last treatment, with infection as a leading cause. Serious adverse reactions occurred in 60%, most often from infection. Adverse reactions occurring in ≥20% of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting. Infection-related adverse reactions occurring in >10% of patients included upper respiratory tract infection, febrile neutropenia, pneumonia, and herpesvirus infection.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

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

EOT=end of treatment; BOR=best overall response; DoR=duration of response; IRC=independent review committee; CR=complete response; PR=partial response; R/R=relapsed or refractory; DLBCL=diffuse large B-cell lymphoma; HSCT=hematopoietic stem cell transplantation; NOS=not otherwise specified.

POLIVY® (polatuzumab vedotin-piiq) for injection, for intravenous use

Initial U.S. Approval: 2019

This is a brief summary of information about POLIVY. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

POLIVY® in combination with bendamustine and a rituximab product (BR) [see Clinical Studies (14)] was approved for the treatment of adult patients with relapsed or refractory DLBCL, who have received ≥2 prior therapies, including a prior CD20-directed monoclonal antibody therapy and whose disease has progressed while on or within 12 months of the completion of prior anti-CD20 therapy. Accelerated approval was granted for this indication based on complete response rate [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

POLIVY can cause peripheral neuropathy, including severe cases. Peripheral neuropathy occurs as early as week 1 and is a cumulative effect [see Adverse Reactions (6.1)]. POLIVY may exacerbate pre-existing peripheral neuropathy.

In Study G029365, of 173 patients treated with POLIVY, 40% reported new or worsening peripheral neuropathy, including 9% a Grade 3 or 4 event. The median time to onset was 21 months (range 0.1 months to 9.7 years). Grade 3 peripheral neuropathy occurred in 8% of patients during treatment for signs of infection. Administer prophylaxis for PML and monitor patients closely throughout the infusion. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management [see Dosage and Administration (2.2)].

5.2 Infusion-Related Reactions

POLIVY can cause infusion-related reactions, including severe cases. Delayed infusion-related reactions as late as 24 hours after receiving POLIVY have occurred. With predmedication, 7% of patients (12/173) in Study G029365 reported infusion-related reactions of any severity during administration of POLIVY. The reactions were Grade 1 in 67%, Grade 2 in 25%, and Grade 3 in 8%.

5.3 Myelosuppression

Treatment with POLIVY can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In patients treated with POLIVY plus BR, Grade 3 or higher neutropenia occurred in 26% of cases, Grade 2 in 12%, and Grade 3 in 2.3%. Periperal neuropathy resulted in POLIVY dose reduction in 2.9% of treated patients; delay in 1.2%, and permanent discontinuation in 2.9%.

5.4 Serious and Opportunistic Infections

In recipients of POLIVY plus BR, adverse reactions leading to treatment discontinuation of all treatment in 31%. The most common adverse reactions leading to treatment discontinuation were thrombocytopenia and/or neutropenia. Table 4 summarizes commonly reported adverse reactions. In recipients of POLIVY plus BR, adverse reactions in ≥5% of patients included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

5.5 Progressive Multifocal Leukoencephalopathy (PML)

POLIVY® (polatuzumab vedotin-piiq) for injection, for intravenous use

Following premedication with an antihistamine and antipyretic, POLIVY 1.8 mg/kg was administered by intravenous infusion on Day 2 of Cycle 1 and on Day 1 of Cycles 2–26, with a cycle length of 21 days.

In recipients of POLIVY (n = 45), the median age was 67 years (range 33 – 86) with 58% being ≥65, 69% were male, 69% white, and 87% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial required an absolute neutrophil count ≥1500/μL, platelet count ≥75,000/μL, creatinine clearance (CrCl) ≥80 mL/min, and bilirubin ≤11.5 times ULN and alanine transaminase (ALT) ≤11.5 times ULN and albumin ≥3 g/dL.

In recipients of POLIVY plus BR, adverse reactions led to dose reduction in 16%, dose interruption in 10% and permanent discontinuation of all treatment in 31%. The most common adverse reactions leading to treatment discontinuation were thrombocytopenia and/or neutropenia. Table 4 summarizes commonly reported adverse reactions. In recipients of POLIVY plus BR, adverse reactions in ≥5% of patients included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

5.6 Hypocalcemia

The most common electrolyte abnormalities in recipients of POLIVY plus BR were hypocalcemia (52%) and hypophosphatemia (9%). Hypocalcemia was the most common electrolyte abnormality. Table 4 provides a summary of laboratory values for patients receiving POLIVY plus BR.

5.7 Laboratory Values

Table 5. Laboratory Abnormalities Worsening from Baseline in Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

5.8 Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential who are pregnant or may become pregnant that there is a potential for fetal harm. Advise females of reproductive potential who are pregnant or may become pregnant to avoid pregnancy and to use effective contraceptive measures during and for at least 12 months after receiving POLIVY. POLIVY is an anti-CD20 antibody and may not reflect the rates observed in practice.

Table 4. Adverse Reactions Occurring in >10% of Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

The table includes a combination of grouped and ungrouped terms. Events were graded using NCIC-CTCAE version 4.03. Events occurring ≥5% of patients in ≥2 events with fatal outcome. Includes 1 event with fatal outcome.

Table 5. Laboratory Abnormalities Worsening from Baseline in Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

Table 1. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 2. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 3. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 4. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 5. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 6. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 7. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 8. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 9. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 10. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 11. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 12. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 13. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 14. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 15. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 16. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 17. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 18. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 19. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 20. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 21. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 22. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 23. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 24. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 25. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 26. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 27. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 28. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 29. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 30. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 31. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 32. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 33. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 34. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 35. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 36. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 37. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 38. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 39. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 40. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 41. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 42. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 43. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 44. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 45. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 46. All Grades, % Grade 3 or 4, % Grade 3 or 4

Table 47. All Grades, % Grade 3 or 4, % Grade 3 or 4
Safety was also evaluated in 173 adult patients with relapsed or refractory lymphoma who received POLIVY, bendamustine, and either a rituximab product or obinutuzumab in Study GO29365, including the 45 patients with DLBCL described above. In the expanded safety population, the median age was 60 years (range 27 – 86). 57% were male, 91% had an ECOG performance status of 0-1, and 32% had a history of peripheral neuropathy at baseline.

Fetal adverse reactions occurred in 4.6% of recipients of POLIVY within 90 days of last treatment, with infection as a leading cause. Serious adverse reactions occurred in 60%, most often from infection.

Table 6 summarizes the most common adverse reactions in the expanded safety population. The overall safety profile was similar to that described above. Adverse reactions in ≤20% of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting. Infusion-related adverse reactions in >10% of patients included upper respiratory tract infection, fever, neutropenia, pneumonia, and herpesvirus infection.

Table 6 Most Common Adverse Reactions (≥20% Any Grade or ≥5% Grade 3 or Higher) in Recipients of POLIVY and Chemoimmunotherapy for Relapsed or Refractory Lymphoma

<table>
<thead>
<tr>
<th>Adverse Reaction by Body System</th>
<th>Grade 1 or 2 (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>30</td>
<td>2.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>2.7</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13</td>
<td>10^a</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6</td>
<td>6^a</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

* Primary prophylaxis with granulocyte colony-stimulating factor was given to 48% of all patients.

** Includes 5 events with fatal outcome. Includes 4 events with fatal outcome.

Other clinically relevant adverse reactions (<20% grade any) included: General disorders: infusions-related reaction (7%), Infection: upper respiratory tract infection (16%), lower respiratory tract infection (10%), herpes virus infection (12%), cytomegalovirus infection (1.2%). Respiratory: dyspnea (5%), pneumonia (1.6%), pyrexia (2.2%). Nervous system disorders: dizziness (10%), Investigations: weight decrease (10%), transaminase elevation (8%), lipase increase (3.5%), Musculoskeletal disorders: arthralgia (7%). Eye disorders: blurred vision (1.2%).

6.2 Immunoactivity

As with all therapeutic proteins, there is a potential for immunoactivity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the occurrence of any 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 to polatuzumab vedotin-piiq in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Across all arms of Study GO29365, 8/134 (6%) patients tested positive for antibodies against polatuzumab vedotin-piiq at one or more post-baseline time points. Across clinical trials, 14/536 (2.6%) evaluable POLIVY-treated patients tested positive for such antibodies at one or more post-baseline time points. In Study GO29365, 6/134 (4.5%) patients tested positive for antibodies against obinutuzumab (1.2%) and 6/134 (4.5%) patients tested positive for antibodies against rituximab (1.2%). Clinical studies of POLIVY did not include sufficient numbers of patients aged ≥65 to determine whether they respond differently from younger patients.

6.3 Hepatic Impairment

Avoid the administration of POLIVY in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN). Patients with moderate or severe hepatic impairment are likely to have increased exposure to MMAE, which can result in increased adverse reactions. POLIVY has not been studied in patients with moderate or severe hepatic impairment (see Clinical Pharmacology (12.3) and Warnings and Precautions (5.7)). No adjustment in the starting dose is required when administering POLIVY to patients with mild hepatic impairment (bilirubin greater than ULN but less than or equal to 1.5 × ULN or AST greater than ULN).

17. PATIENT COUNSELING INFORMATION

17.1 Peripheral Neurotoxicity

Advise patients that POLIVY can cause peripheral neuropathy. Advise patients to report to their healthcare provider any numbness or tingling of the hands or feet or any muscle weakness (see Warnings and Precautions (5.1)).

Infusion-Related Reactions

Advise patients to contact their healthcare provider if they experience signs and symptoms of infusion reactions, including fever, chills, rash or breathing problems within 24 hours of infusion (see Warnings and Precautions (5.2)).

Myelosuppression

Advise patients to report signs or symptoms of bleeding or infection immediately. Advise patients of the need for periodic monitoring of blood counts (see Warnings and Precautions (5.9)).

Infections

Advise patients to contact their healthcare provider if a fever of 38°C (100.4°F) or greater or other evidence of potential infection such as chills, cough, or pain on urination develops. Advise patients of the need for periodic monitoring of blood counts (see Warnings and Precautions (5.4)).

Progressive Multifocal Leukencephalopathy

Advise patients to seek immediate medical attention for new or changes in neurological symptoms such as confusion, dizziness, or loss of balance; difficulty talking or walking; or changes in vision (see Warnings and Precautions (5.5)).

Tumor Lysis Syndrome

Advise patients to seek immediate medical attention for symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy (see Warnings and Precautions (5.6)).

Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice (see Warnings and Precautions (5.7)).

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose (see Use in Specific Populations (8.3)).

8.3 Females and Males of Reproductive Potential

Advise females of reproductive potential, and males with female partners of reproductive potential, to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose (see Use in Specific Populations (8.3)).
Roundtable Discussion: Kandra Explores Benefit of Chemoimmunotherapy for Small Cell Lung Cancer

**CASE SUMMARY**

A woman, aged 73 years, presented with shortness of breath, productive cough, chest pain, fatigue, anorexia, and recent 18-lb weight loss. She had a history of hypertension and a 45 pack-year smoking history. She still smokes. A physical examination revealed dullness to percussion and decreased breath sounds. Chest x-ray then showed a left hilar mass and a 5.4-cm left upper lobe (LUL) mass. A chest-abdomen-pelvis CT scan revealed hilar mass with bilateral mediastinal extension but results were negative for distant metastatic disease. A PET scan showed activity in the LUL mass, supraclavicular nodal areas, and liver lesions. One small brain lesion was seen in MRI but was deemed asymptomatic. An interventional radiology biopsy of the liver confirmed she had small cell lung cancer (SCLC). She had an ECOG performance status of 1.

**DISCUSSION QUESTION**

What are the greatest challenges and unmet needs when treating patients with extensive-stage SCLC (ES-SCLC)?

**BADIN:** One major thing we do not have is a target we can go after, unlike with non–small cell lung cancer [NSCLC]. We do have a driver mutation and subtypes. Today, we still lump all SCLCs under 1 umbrella. I am hoping that soon, for clinical research purposes, we can have better understanding, better subtyping, targeted treatments, and appropriate treatments for patients. Another challenge is these patients are usually sicker than patients with NSCLC.

All of them are smokers with multiple comorbidities. The prevalence of CNS [central nervous system] disease and brain metastases is also a challenge. It is a very difficult disease to treat in general, so [there are] a lot of unmet needs there.

**KONALA:** The only reason is if I need to start a patient and if we need to treat them in the hospital. I then use chemotherapy first and start immunotherapy from the second cycle. Other than that, most patients I treat in my clinic get immunotherapy up front.

**KANDRA:** Excellent point. So, you basically add immunotherapy at a later point, not in the hospital?

**KONALA:** Yes. You cannot use it in the hospital.

**KANDRA:** That is a fairly common problem because you cannot get immunotherapy from the inpatient pharmacy inventory. Part of it is the cost associated with that.

**MULHERIN:** The only thing I think of is whether they had a severe autoimmune disease where you would not consider giving immunotherapy. I have
never seen that in SCLC. I have seen a couple of patients with NSCLC who might have had granulomatosis with polyangiitis, or I had a patient who had lupus cerebritis—very unfortunate. But never in SCLC. It does not tend to go together.

**MUTHUSAMY:** We do come across patients with rheumatoid arthritis or lupus getting lung cancer. You must be careful treating them.

**MULHERIN:** You should be careful and have a risk-benefit discussion with a rheumatologist so everyone is informed and they can be monitored. In general, before I consider not giving immunotherapy, it must be a severe condition.

**MUTHUSAMY:** I treated a patient with rheumatoid arthritis. He did not have any exacerbation of the rheumatoid arthritis with the immunotherapy. I do not know how common exacerbation of the autoimmune disease is. Does anybody else have experiences like that?

**MULHERIN:** I have with NSCLC but not with SCLC.

**KANDRA:** That seems to be the case for well-controlled rheumatoid arthritis without any active immunosuppression. That seems reasonable to try considering the risks and benefits if you have a discussion with the patient, but when patients are on strong immunosuppressive therapy for rheumatoid arthritis, you are talking about a different scenario. With those cases, I doubt we would be pushing for immunotherapy.

**WALLING:** I have had 2 patients with MS [multiple sclerosis], if you consider that an autoimmune condition, 1 with NSCLC, and 1 with ES-SCLC. Our doctors of pharmacy did not recommend giving immunotherapy because there were case reports of deaths with MS. I do not know about rheumatoid arthritis, even though they were not included in the analysis.

**KANDRA:** Absolutely. It is a rare situation to see patients with MS, but there are contraindications, and I have not used immunotherapy in that setting.

**ANWAR:** That is my experience too. I do not have any patients with an autoimmune disease, but in my discussions with colleagues, MS is a total contraindication, as is anything that involves the brain or high immunosuppressive medication. Otherwise, for controlled rheumatoid arthritis, individuals have used it.

**MULHERIN:** Another one might be if they have had a solid organ transplant. They had immunosuppressants. So obviously, many of those patients were excluded from trials. In our center [Hematology Oncology of Indiana], there is a large renal transplant program, for example. There are case reports of these patients experiencing rapid allograft rejection. Again, it is SCLC, so a risk-benefit discussion with the transplanting physician is needed.

**KANDRA:** You are right. And they do have these on the black box warnings, on the labels, for all these immunotherapy drugs at this point. So, all excellent points.

**BADIN:** Sometimes, for small cell cancer of the GI [gastrointestinal] tract or GU [genitourinary] primary cancer, it might be challenging to get it approved by the insurance. I know we are discussing lung cancer, but we all sometimes see small cell cancer of the prostate and small cell cancer of the colon, and the insurance may not want to cover it sometimes.

**DISCUSSION QUESTION**

What additional work-up, if any, would you order to inform your treatment recommendation?

**MUTHUSAMY:** [Most work-up] was already done, including an MRI of the brain. Maybe a PET scan [should be done]?

**KANDRA:** If it were not SCLC, I am sure we would all be doing something different. We would be ordering more molecular studies, correct?

**MUTHUSAMY:** Correct.

**MULHERIN:** Right, but for SCLC there is little else to do unless you are going to send the patient for a clinical trial.

**MUTHUSAMY:** This patient did not have PET scans. Is there any role for a PET scan under the circumstances? She already has stage IV disease with a solitary asymptomatic brain metastasis smaller than 2 cm.

**MAHESHWARI:** It all depends on what kind of diagnosis we put in the computer. If we write “SCLC,” insurance will not approve it. If we write “lung cancer,” then they will approve the PET scan.

**MUTHUSAMY:** Yes, the International Classification of Diseases [ICD] code makes a difference. The artificial intelligence is not that good to discriminate all these things.
“Lung cancer” will be the generic global ICD code that might get you through a lot of things, yes.

KANDRA: I think you are all correct. It is difficult to get approval, but another thing I found helpful is if you put it as a high-grade neuroendocrine tumor, they will accept it, and you can get that scan done. We have been in those situations where we felt like a PET scan would be helpful in defining whether that adrenal lesion or that liver lesion is hypermetabolic, and we wanted to avoid another biopsy.

DISCUSSION QUESTIONS

• What would be your approach toward treating this patient at this point?
• What factors influence your recommendation?
• How would you counsel this patient regarding the treatment options?
• What do you consider the most important points to communicate?

KONALA: Choosing either atezolizumab [Tecentriq] or durvalumab [Imfinzi] is fine. But in the clinical trials, the difference is that you use 4 cycles of chemotherapy with atezolizumab and you can go up to 6 cycles with durvalumab.

I think [the IMPower133 trial (NCT02763579) of atezolizumab] did not include patients with brain metastases. I would use a chemoimmunotherapy combination. I do not know how many are using trilaciclib [Cosela], or sometimes we use growth factors in these patients.

MULHERIN: In the CASPIAN trial [NCT03043872] of durvalumab, you could have your choice of platinum-based agents, whether cisplatin or carboplatin. I do not use cisplatin if they have metastatic disease—if they are not going to be cured. It is not going to change things substantially. It is probably whatever you feel most comfortable with. Maybe insurance has a preference. I think the data are comparable.

MUTHUSAMY: I think there aren’t any trials with 3-year data available. Even the atezolizumab trial does not have those data published yet.

KANDRA: We have the choice of these 2 immunotherapies, as you all mentioned.

MUTHUSAMY: But I think we all have more experience with atezolizumab than with durvalumab, unless you were in the trial, because durvalumab was just approved in the last couple of years.

KANDRA: Yes, I think it is more like a habit. The first one you start using, you become very comfortable with it. You see some good results. You want to keep going. You do not want to change anything.

How do you decide between carboplatin and cisplatin when using an immune checkpoint inhibitor [ICI]-chemotherapy regimen for SCLC? How important is the platinum agent in your regimen selection?

ANWAR: I think most oncologists in the United States use carboplatin in metastatic settings, just for lesser toxicity.

KANDRA: Absolutely. Less renal toxicity, less ototoxicity, and less nausea with the carboplatin.

MULHERIN: There are no data [suggesting] that they are going to have improved survival in this disease by using cisplatin. So, it is far more toxic.

KANDRA: Absolutely. The only advantage of cisplatin over carboplatin, I would say, is less myelosuppression, and I do not know whether you run into that scenario as much in the first line.

CASE UPDATE

The patient started on concurrent atezolizumab with carboplatin/etoposide and has completed 4 cycles.

DISCUSSION QUESTION

What data support the addition of an ICI to platinum/etoposide chemotherapy?

MUTHUSAMY: Progression-free survival [PFS] is increased in both trials. So, combined chemoimmunotherapy seems to be better than chemotherapy alone. It offers better PFS.

MAHESHWARI: Should we give 4 cycles or 6 cycles?

MUTHUSAMY: I just follow the protocol, so 4 cycles is the standard protocol unless the patients keep responding. At least for old-timers like me, if the patients keep responding, I may give additional cycles.

MAHESHWARI: The general rule is, if the patient has significant residual disease and has been responding with a partial response [PR] after 4 cycles, I personally push for 5 or 6 cycles.
MUTHUSAMY: If the patient’s performance status and protoplasm [are] good enough, they may be able to handle 2 more cycles. We should push for minimal disease, theoretically, we can assume immunotherapy is very effective if you have a low tumor burden.

MAHESHWARI: I have 2 patients [for whom] immunotherapy caused a significant disseminated skin rash. I had to stop treatment. Those patients are around 2 years out, still living. I still believe anybody who has a great response but a lot of toxicity from immunotherapy will probably have long or durable responses.

KANDRA: These are excellent points, and we come across this question so often, whether to stop at 4 cycles or go off protocol and do 6. We know that for patients with tremendous tumor burden, bad paraneoplastic syndromes, and high-volume disease, that chemotherapy works. But if you follow the data from the trials, we are supposed to do 4 cycles, but I have certainly seen a lot of oncologists go up to 6 cycles in certain patients.

MAHESHWARI: I do not give [patients only] 4 cycles in ES-SCLC. I treat to the maximum response, 4, 5, or 6 cycles.

KANDRA: The protocols recommend a CT scan at the end of 4 cycles. That may be a point where you reassess, see what the disease burden is, and then make an individualized decision with the patient and explain that the trial says 4 cycles of chemotherapy but we can decide to do 6. Again, that would be considered off-label. Anything else? Dr Raghavan, I am sure you have had a lot of experience.

RAGHAVAN: I would say not with immunotherapy; 4 cycles of chemotherapy is probably because you are using maintenance with the immunotherapy anyway. When we did not have immunotherapy, we were giving 4 and 6 cycles of chemotherapy.

ZAYDAN: Do you have any idea how they decided on 4 cycles when they designed the study?

KANDRA: I never understood the logic behind that. The standard is 4 to 6 cycles, and maybe they are trying to avoid extra toxicities by adding the immunotherapy. Maybe they were not as sure about the volume of treatment the patient can tolerate when adding something. The strategy might be to cut back on something else.

ANWAR: It may be interesting to see whether the control arm had 4 cycles or 4 to 6 cycles.

MUTHUSAMY: CASPIAN [NCT03043872] allowed 6 cycles whereas IMpower133 only allowed 4 cycles in the control arm.

DISCUSSION QUESTION

What is your reaction to the IMpower133 data? Has this regimen affected your practice? If so, how?

MUTHUSAMY: We want something rather than the current chemotherapy, but it is not a fantastic home run; the HRs were all close to 1, [including] 0.96 [for a subgroup]. I am not sure what that means; the average is [0.76] and the $P$ value is .01. I am not sure whether the HR means anything if the $P$ value is .01.

KANDRA: You raise a valid point. Yes, we need something more in SCLC; there are so many unmet needs in SCLC, and that reflects in our opinions on the results of these trials. We certainly want to see more substantial benefit and even more drastic HRs, but that has not happened. Yes, the HR is close to 1 in the subgroup of patients with brain metastases.

MUTHUSAMY: Even the overall HR [of 0.76] has a $P$ value of .01, [meaning that] even if 2 patients got better, it would look like the HR is good. But the $P$ value should be [more] significant. The $P$ value in this study is .01. [However], the 1-year and 2-year overall survival [OS] rates are better than chemotherapy, and that is very encouraging.

KANDRA: When we look at those subgroups, we cannot draw statistical conclusions. The trials are not powered to have strong statistical data. We use them to [ask], “Are we learning something in each of these subgroups? Can we apply these data into our practice? Or can we do more trials to know more about what we are seeing?”

MULHERIN: It is depressing that this is probably the biggest advance in SCLC in the past 30 years. That is a 2-month OS advantage. [The chemotherapy regimen] is from the 1980s and probably the most significant advantage is the improvement in supportive medications like antiemetics.

[Chemoimmunotherapy] is better, and I was enthusiastic when I started using it, but patients with brain metastases do worse overall. Is that because they are on steroids? Are the steroids negating the treatment? There are all kinds of things you could try to analyze, but regardless, it is what it is. These are the best tools we have available. If they have brain metastases, they need to get radiotherapy.
MUTHUSAMY: Yes. That is why we are using this regimen.

DISCUSSION QUESTION

What is your reaction to the updated CASPIAN analysis? Does it affect your practice?

MUTHUSAMY: They have clear 3-year data, and the Kaplan-Meier curve is much more open than the IMpower133 Kaplan-Meier curve. I can see much more separation [between experimental and control arms] in CASPIAN than in IMpower133.\(^6,7\) I think durvalumab seems to be appealing based on this 3-year report [Table\(^7,8\)]. Hopefully, the atezolizumab data will be released soon enough, so we can see the differences between those 2 regimens.

KANDRA: Yes, I would be very eager to look at what the latter part of the follow-up shows.

NIDHIRY: I agree that there is a longer follow-up with CASPIAN and durvalumab, but I feel that the benefits are still comparable. Although it is not a head-to-head study, there is some modest benefit with addition of immunotherapy to chemotherapy in this disease, but the overall outcome is still poor. We reach for that because we do not have better treatment options. We go with what we have. I feel that either option will be reasonable in the setting.

KANDRA: Do you have other input as to the data about the brain metastases? Do you think one is superior to the other?

BARAI: The survival data certainly seem interesting with this combination. I think I will tend to give it a use, and a longer-term follow-up is also appropriate to see the benefits.

KANDRA: What does anyone think about using 6 cycles vs 4 cycles in the control arm? Is that important when you are making any conclusions as to what the real-world experience is?

BARAI: That depends on the patient situation. It is understandable that when a clinical trial is going on, you want to have a certain defined [duration]. During the actual patient situation, if the patient has an 80% or so response with heavy disease, you are not going to stop at 4 cycles [if] the benefit is continuing to accrue and the patient is able to tolerate it. Sometimes we try to blindly follow the trial data, but the trial has a certain defined situation when they want to be able to analyze it.

ANWAR: You can make the other case too. The control arm got 6 cycles, while the immunotherapy arm got 4 cycles, and still those 6 cycles did not show any improvement. If you look at the 2 trials, the PFS was the same with atezolizumab as well as with durvalumab.\(^2,3\) So, I am not sure whether the addition of 2 cycles is making any difference in the treatment. You can use it in certain cases.

MUTHUSAMY: Did they look at the stratification of complete responses [CRs] and PRs? Did they do any differently between each arm?

KANDRA: They did break it down to CRs vs PRs. I believe patients with CRs are still less than 10% in both trials.\(^2,3\) But the [PR rate] is much higher in the durvalumab trial at around 66%.

MUTHUSAMY: Did the patients with CRs do a lot better than those with PRs? If it is a 10% response, only 26 out of 260 patients would have CRs in the trial.

KANDRA: I think based on our overall experiences with any other cancers or any other trials, generally patients with CRs tend to have much longer disease-free intervals and better overall outcomes. I do not think we can [conclude] a lot about these specific data, but in general we all like CRs.

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

### TABLE. Overall Survival in the CASPIAN Trial (NCT03043872)\(^7,8, a\)

<table>
<thead>
<tr>
<th></th>
<th>DURVALUMAB PLUS PLATINUM/ETOPOSIDE</th>
<th>PLATINUM/ETOPOSIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>12.9 (11.3-14.7)</td>
<td>10.5 (9.3-11.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.71 (0.60-0.86; ( P = .0003 ) [nominal])</td>
<td></td>
</tr>
<tr>
<td>12-month OS rate</td>
<td>52.8%</td>
<td>39.3%</td>
</tr>
<tr>
<td>18-month OS rate</td>
<td>32.0%</td>
<td>24.8%</td>
</tr>
<tr>
<td>24-month OS rate</td>
<td>22.9%</td>
<td>13.9%</td>
</tr>
<tr>
<td>36-month OS rate</td>
<td>17.6%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

OS, overall survival.

\(^a\) Median follow-up: 39.4 months
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Kd=Kyprolis (carfilzomib) and dexamethasone