Case-Based Roundtable Meetings SPOTLIGHT
FEBRUARY 2022 | VOL. 5 | NO. 3

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The Case-Based Roundtable Meetings Spotlight covers a series of oncology education roundtable meetings for practicing oncologists led by expert physicians presenting case-based data across cancer types.

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For a patient who has a recent change, drop, or stop in the immunosuppression agents and comes in with rash or diarrhea, think about GVHD.”

—UDAY R. POPAT, MD

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TargetedOnc.com/link/1573
## munoz covers multiple regimens for the treatment of dlbcl

### case

A 75-year-old man presented with fever, a 7-lb unintentional weight loss, and occasional chest pain. Medical history: hypertension, medically controlled; cardiac failure; atrial fibrillation. Physical exam: appeared tired; palpable bilateral cervical lymphadenopathy. Laboratory results:
- Lactate dehydrogenase: 300 U/L
- Hemoglobin: 10.8 g/dL
- Bilirubin: 1.7 mg/dL
- Creatinine: 1.7 mg/dL
  - All other values: within normal limits
- HIV/hepatitis B/C: negative

Lymph node biopsy:
- Immunohistochemistry panel: CD10+ and CD20+ confirmed diffuse large B-cell lymphoma (DLBCL), germinal B-cell–like subtype
- Fluorescence in situ hybridization: negative for rearrangements of BCL6, BCL2, and MYC

Imaging studies:
- Whole-body PET/CT scan showed activity in multiple lymph nodes above and below the diaphragm (largest node, 3.9 cm) and evidence of subcutaneous tissue involvement
- MRI of the brain showed no evidence of lesions.

- Staging: stage IV; International Prognostic Index (IPI), high risk; Ann Arbor stage III/IV
- ECOG performance status: 1
- The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone), which was well tolerated.
- A PET scan at the end of treatment showed complete remission (CR).
- One year later, the patient presented with diffuse lymphadenopathy, confirmed by PET/CT scan.
- Biopsy showed relapse of DLBCL.
- The patient was considered ineligible for transplant.
- He received R-GemOx (rituximab, gemcitabine, and oxaliplatin) and achieved a partial response (PR).
- Five months later, he presented with overt disease progression.

### targeted oncology™: based on your experience, is chimeric antigen receptor (CAR) T-cell therapy worthwhile for patients?

**munoz:** The overall response rate [ORR] is somewhere between 50% and 80%.1-3 But what you care about in someone with an aggressive disease is a CR. [This means] no evidence of disease [and] everything that was abnormal before the CAR T cells becomes normal after the CAR T cells, whether it’s bone marrow involvement, a PET scan, or whatever that may be. CR rates are somewhere between 40% and 50%.1-3 Now, it’s tempting to look at the numbers and say, “Well, maybe one is a little better than the other.” I try not to do that because there’s [no] randomized trial comparing axi-cel [axicabtagene ciloleucel (Yescarta)] vs tisa-cel [tisagenlecleucel (Kymriah)] or liso-cel [lisocabtagene maraleucel (Breyanzi)]. So this is not apples vs oranges, but perhaps it’s a green apple vs a red apple.

They are not exactly the same, they’re a little bit different. I think the 3 of them work, the 3 of them have similar toxicities. [With] axi-cel, for example, the median overall survival has not been reached [in the ZUMA-1 trial (NCT02348216)].1 And when it comes to tisa-cel, [the median overall survival in JULIET (NCT02445248)] was 12 months.2 When it comes to liso-cel [in TRANSCEND-NHL-001 (NCT02631044)], it was 21.1 months.3 Again, this is the
median, but if you truly look at the patients that achieved CR, you can see that the Kaplan-Meier curves plateau. In the wording for the recent FDA approval for liso-cel, based on how the trial was designed, you will see some differences. For example, primary mediastinal lymphoma was allowed for liso-cel and it was also allowed for axi-cel. It was not part of the inclusion criteria for tisa-cel so that is why, for that particular construct, you should not prescribe tisa-cel, but this is just a reflection of how the trial was designed.

What kind of toxicity do we see with these regimens? Now, this is not a walk in the park. You can have severe toxicity, even lethality, and you could see fatalities. In the axi-cel trial of ZUMA-1, [slightly] more than 100 patients enrolled. Three patients suddenly had grade 5 toxicity; it’s a minority of patients but it can happen, and because of that you need to [counsel] the patients that there could be a lethal outcome. And when it comes to the toxicity, frameshift [seems to have occurred].

The first wave is cytokine storm. Then once that wave starts to get better—it’s not immediate, usually starts from day 2—it peaks around day 4 or 5 and then starts to trend down. Just when the patients are starting to get better from that, you start seeing, as I said,....frameshift; you start seeing the second wave of toxicity, which would be neurologic toxicity.

We don’t understand why this happens because there’s no CD19 in the brain, for example. It’s probably interleukin mediated. You have this overwhelming amount of cytokines and interleukins that probably are going to get into your CSF [cerebrospinal fluid], and they are going to cause trouble. Now, what are the chances of having this severe cytokine storm? You have 2% for liso-cel and 11% for axi-cel. When it comes to neurologic toxicity, it’s 10% for liso-cel, 11% for tisa-cel, and 32% for axi-cel. Again, these are not randomized trials, so even though it’s tempting to look at those numbers and come up with strong conclusions, it always gives me pause to do that.

When it comes to CAR T cells, including managing the cytokine storm, you need to have at least 2 tocilizumab [Actemra] doses for each patient [for whom] you are going to prescribe CAR T cells. We’re facing a dosage shortage because [the drug was] also approved for COVID-19. People are using tocilizumab left and right in these institutions that have CAR T cells and you don’t have enough for your patients receiving CAR T cells so that is causing problems.

I highlight [the issue of] prolonged cytopenias. [The regimen is] not for everyone; not every patient is going to go into CR. It’s almost like tossing a coin; it’s around 50%. So what happens for the patients that do not achieve remission and eventually progress? Sometimes they do have low counts, and that, in my clinic, is an obstacle to enrolling them in clinical trials subsequently. Those counts are still lingering a little bit on the low side, and that is challenging sometimes because they do not meet the inclusion criteria for the next trial you are thinking about.

Finally, if you prescribe a very strong anti-CD19 CAR T cell, you are going to cause B-cell aplasia. You’re going to obliterate the B cells, the normal B cells too, and this is going to cause low gamma globulins. These patients are going to be committed to IVIG [intravenous immunoglobulin] for life, and this is very expensive and is going to be troublesome for them.

We have seen that maybe 20% to 25% of patients require IVIG, and usually it’s for a brief period of time. Why? I think that is the poor man’s way...of looking at the persistence of the CAR T cells. It’s possible that they are not present for life, and as those CAR T cells start not being active anymore, your normal B cells start to come back, and that is why a patient that could need, briefly, IVIG, may not require it for life. Something that is documented in the trial, something that I have seen in my own personal practice, is that only a minority of patients post CAR T cells actually require IVIG. I would say most of them do not require it [long term], they require it for a brief period of time. Eventually the CAR T-cell persistence goes away and the normal B cells start to come back.

Do you need CAR T cells for life? I don’t know; I personally do not think so. I think you need the CAR T cells for as long as they do their job. If you have them floating around in your bloodstream for 6 months, and during those 6 months they obliterate all the cancer cells, good job. You do not need them for life. We know, based on the [National Institutes of Health] experience, that they have patients more than a decade after receiving CAR T cells [in whom] you cannot find persistent CAR T cells...they’re still in remission. They probably destroyed all the cancer cells during that brief period of time when the CAR T cells were active.

**POLLING QUESTION**

During a live virtual event, Munoz asked participants, “What would you most likely recommend for this patient in the third-line setting after chemoimmunotherapy?”

- Polatuzumab vedotin ± bendamustine/rituximab 46% (5)
- Tafasitamab + lenalidomide 36% (4)
- Loncastuximab tesirine 9% (1)
- Selinexor 9% (1)
- Other 0% (0)

**TOTAL VOTES: 11**
What do you think of the options for this patient?

Let’s talk about lonca-T [loncastuximab tesirine (Zynlonta)]. It’s important always to [look at] the verbiage of the label because this is what is going to allow you to prescribe it. To be fair and balanced, I’m going to discuss...all of the options so you [can decide...which one you would] want to choose with your patients. It’s an anti–CD19-directed antibody and [approved for] DLBCL, after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and also high-grade BCL.° Lonca-T, in theory, is the one that is giving you that option, or at least it was studied in very few patients that have that double-hit and triple-hit lymphoma.

Again, this is an antibody-drug conjugate, similar to brentuximab vedotin [Adcetris] but brentuximab acts against CD30. Lonca-T is targeting CD19 and the payload is pyrrolobenzodiazepine for this particular agent. The trial [for lonca-T in relapsed/refractory DLBCL] was called LOTIS-2 [NCT03589469].° Patients with 2 or more lines of [previous] systemic therapy [were enrolled] and needed to have CD19 positivity via biopsy, particularly prior anti-CD19 therapy, and this medication [was prescribed] as a 30-minute infusion every 3 weeks for up to a year. You want to pack a punch so you start with a little bit of a higher dose for the initial 2 cycles. After those initial 2 cycles, you go with a lower dose, and then you use a maintenance dose follow-up every 12 weeks for up to 3 years. The primary end point was ORR and they looked at many other variables.

Let’s look at the phenotype of the patients that enrolled. Age is something important: median was 66 years.° The oldest patient was 71 years old and 10% of patients had double- or triple-hit lymphoma. And that is why this made it all the way to the label, allowing you to prescribe lonca-T in this population. Again, not a dramatic number of patients with double- or triple-hit [lymphoma] but there were some, and that is why you do have some evidence of seeing some improvement in this population.

The median number of prior systemic therapies was 3.° The highest number was 4, so again, this population of patients was not heavily pretreated as we have seen in other patients. But I don’t think that they were cherry-pick- ing, necessarily, because 58% of patients were refractory to the last line of therapy and 14% of patients had received a prior autologous stem cell transplant. Only 1 patient had received a prior allogeneic transplant.

What was the efficacy seen in LOTIS-2?

The primary end point was ORR—easy to remember because it’s 48% and that was half CR and half PR [95% CI, 39.9–56.7%].° Every time I look at aggressive lymphomas, I try to zero in on CR because that is where I want to take those patients with aggressive disease. Median time to first response was 41 days so it’s not necessarily immediate, and the mean number of cycles that patients with lonca-T received was 4.5, so again, it’s not a therapy that will necessarily last forever. The minimum [number of cycles] was 1, in a patient that progressed quickly. The maximum that someone received was 18 cycles. Something [that should be] highlighted is whether or not [lonca-T is effective in patients who] have had a transplant before, [and] this medication seems to work even in high-risk subgroups.

The median duration of response was 13.4 months, so that is decent for a treatment that you could prescribe off the shelf in your clinics.° The median duration of response for patients that achieve CR has not been reached, so that is pretty decent in a study that allowed patients that had high-risk features. About that controversy, if patients can receive subsequent therapies that also are attacking CD19, again, when you have a hammer, everything looks like a nail. So it’s very tempting, with so many anti-CD19 maneuvers, to keep just hammering down the CD19. [There’s] nothing surprising there; we have done that with the anti-CD19 [and we have done that against CD20 for the longest time. After chemotherapy A fails, we use chemotherapy B, and we plug in another anti-CD19 or anti-CD20 treatment. So it’s not surprising to do this, and these companies are starting to generate some data to back up that story.

In 15 patients who received CD19 there are active CAR T cells after lonca-T, which isn’t anti-CD19 treatment, and they saw an ORR of 46.7% so [patients] can still respond.° It seems that they can still respond to an anti-CD19 CAR T cell even if you have used an anti-CD19 treatment previously. Nine patients proceeded to stem cell transplant as consolidation after lonca-T.

How did patients do in terms of AEs related to lonca-T?

There was a little...atypical toxicity, something that is a little bit unique, which was peripheral edema.° [Stratified by age group, the results in those younger] than 65 years...was 16.9% and in those older than 65, it was 22%. Overall, 20% of patients had peripheral edema. [Many of the most common treatment-related adverse events were hematologic in nature, which is] pretty much as expected, right?

These patients have received R-CHOP and/or R-GemOx before...so it’s not surprising that low counts are something that you are going to see commonly. The most commonly seen grade 3 or higher treatment-related adverse events, or treatment-emergent adverse events, were neutropenia, thrombocytopenia, and anemia, so no
**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.

**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.

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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 4% and 2% of patients with DTC and 2% of patients with HCC, respectively. 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 based on severity.

**Proteinuria.** 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 hepatoportal 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.

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Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter 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.

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

**See a spectrum of results**

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

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

**LENVIMA + everolimus is the only TKI-mTOR inhibitor combination following anti-angiogenic therapy in advanced RCC**

**Results** of second-line advanced RCC

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

**Selected Safety Information**

**Warnings and Precautions**

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• 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm.
  — 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus alone.
  — Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus alone.
• The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs with an observed HR of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm.
• Study 205 randomized 153 patients with advanced or metastatic renal cell carcinoma who had previously received anti-angiogenic therapy 1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (<10 mg/dL vs ≥10 mg/dL vs <10 mg/dL vs ≥10.5 g/dL vs >10.5 g/dL for males and <13 g/dL vs ≥13 g/dL vs >13 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other efficacy outcome measures included overall survival and objective response rate.

**SELECTED SAFETY INFORMATION**

**Warnings and Precautions (cont'd)**

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

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

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class 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.

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**14.6-month median PFS:** with LENVIMA + everolimus vs everolimus alone

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<th>Time (months)</th>
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**REDUCTION IN THE RISK OF PROGRESSION OR DEATH WITH LENVIMA + EVEROLIMUS VS EVEROLIMUS ALONE**

<table>
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<th>Treatment</th>
<th>Median (95% CI)</th>
<th>HR: 0.37 (95% CI: 0.22-0.62)</th>
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<tbody>
<tr>
<td>LENVIMA (18 mg) + everolimus (5 mg)</td>
<td>14.6 months</td>
<td>63%</td>
</tr>
<tr>
<td>Everolimus (10 mg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus-treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

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

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 38% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH level >0.5 mU/L 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%), diabetes (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 85% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), 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 breastfeeding infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

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

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

- Differentiated Thyroid Cancer (DTC)
  - For the treatment of patients with locally recurrent or metastatic, progressive, radioidine-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 endometrial carcinoma (EC) that is not microsatellite instability-high (MSI-H) 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.

**DOSEAGE 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 24 mg orally once daily.
- **HCC:** The recommended dosage is 18 mg orally once daily for patients 80 kg and 8 mg orally once daily for patients less than 60 kg.
- **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.
- **RCC:** 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.
- **DTC:** 18 mg orally once daily with everolimus 5 mg orally once daily.

**Dosage Modifications for Adverse Reactions:** Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage modifications for LENVIMA for adverse reactions.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modifications for LENVIMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Grade 3</td>
<td>Withhold for Grade 3 that persists despite optimal antihypertensive therapy.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Cardiac Dysfunction</td>
<td>Grade 3</td>
<td>Withhold until improvement to Grade 0 to 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either resume at a reduced dose or discontinue depending on severity and persistence of cardiac dysfunction.</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 improvement to Grade 0 to 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either resume at a reduced dose or discontinue depending on severity and persistence of hepatic toxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue for severe hepatic toxicity.</td>
</tr>
<tr>
<td>Renal Failure or Impairment</td>
<td>Grade 3 or 4</td>
<td>Withhold until improvement to Grade 0 to 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 g or greater proteinuria in 24 hours</td>
<td>Withhold until less than or equal to 2 grams of proteinuria per 24 hours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue for nephrotic syndrome.</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Fistula Formation</td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Greater than 500 ms or greater than 60 ms increase from baseline</td>
<td>Withhold until improvement to less than or equal to 488 ms or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
<tr>
<td>Reversible Posterior Leukoencephalopathy Syndrome</td>
<td>Any Grade</td>
<td>Withhold until fully resolved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Persistent or intolerable Grade 3 or 4 adverse reaction</td>
<td>Withhold until improvement to Grade 0 to 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume at a reduced dose.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Indicator</th>
<th>First Dose Reduction To</th>
<th>Second Dose Reduction To</th>
<th>Third Dose Reduction To</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTC</td>
<td>20 mg once daily</td>
<td>14 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>RCC</td>
<td>14 mg once daily</td>
<td>10 mg once daily</td>
<td>8 mg once daily</td>
</tr>
<tr>
<td>EC</td>
<td>14 mg once daily</td>
<td>10 mg once daily</td>
<td>8 mg once daily</td>
</tr>
<tr>
<td>HCC</td>
<td>10 mg once daily</td>
<td>4 mg once daily</td>
<td>4 mg every other day</td>
</tr>
</tbody>
</table>

**Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Pembrolizumab**

- When administering LENVIMA in combination with pembrolizumab, modify the dosage of one or both drugs as appropriate.
- Withhold, dose reduce, or discontinue LENVIMA as shown in Table 1. Refer to pembrolizumab prescribing information for additional dose modification information.

**Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Everolimus**

- When administering LENVIMA in combination with everolimus, withhold or reduce the LENVIMA dose first and then the everolimus dose for adverse reactions of both LENVIMA and everolimus. Refer to the everolimus prescribing information for additional dose modification information.

**Dosage Modifications for Severe Renal Impairment**

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

- **DTC:** Dialyzed thyroid cancer: 14 mg orally once daily
- **RCC:** Renal cell carcinoma: 10 mg orally once daily
- **Endometrial carcinoma:** 10 mg orally once daily

**Dosage Modifications for Severe Hepatic Impairment**

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

- **DTC:** Dialyzed thyroid cancer: 14 mg taken orally once daily
- **RCC:** Renal cell carcinoma: 10 mg taken orally once daily
- **Endometrial carcinoma:** 10 mg orally once daily

**Preparation and Administration**

LENVIMA capsules can be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, put capsules into 1 tablespoon of water or apple juice without breaking or crushing the capsules. Leave the2 tablet to dissolve completely in water or apple juice for at least 10 minutes and discard any unabsorbed tablets after 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swill the contents a few times and swallow the water or apple juice.

**DOSE FORMS AND STRENGTHS**

- 4 mg: yellowish red body and yellowish red cap, marked in black ink with “E” on cap and “LEN 4 mg” on body.
- 8 mg: yellow body and yellowish red cap, marked in black ink with “E” on cap and “LEN 8 mg” on body.

**CONTRAINDICATIONS**

None.

**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 16 days in SELECT and 26 days in REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred in 17% in 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 25 days. Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure of more than 180 mmHg or diastolic blood pressure greater than or equal to 100 mmHg occurred in 21%.

**Cardiac Dysfunction**

Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 798 patients with DTC, RCC, or HCC, Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, cardiac failure, ventricular hypertrophy, or decrease in left or right ventricular ejection fraction of more than 20% from baseline) occurred in 3% of LENVIMA-treated patients. Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and reduce at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

**Arterial Thromboembolic Events**

Arterial thromboembolic events (arterial thromboembolism) in patients receiving LENVIMA with everolimus, arterial thromboembolism in 4% of patients in SELECT (DTC), 2% in 24% of patients in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

**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 24% of patients receiving LENVIMA in REFLECT (HCC). Grade 3 to 5 renal failure or impairment was reported in 3% (DTC) and 2% (HCC) of patients, including 1 fatally in each study. In Study 205 (RCC), renal impairement or failure was occurred in 18% of patients receiving LENVIMA with everolimus, including 3% in 10% of patients. Initiate prompt management of diuresis or dehydration/hypovolemia. Withhold and reduce 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% in SELECT (DTC) and REFLECT (HCC), respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA with everolimus and in 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus.

**Diabetes**

The 937 patients treated with LENVIMA in SELECT (DTC) and REFLECT (HCC), diabetes occurred in 4% of patients, including 3% diabates in 6%.

**Diabetes**

In Study 205 (RCC), diabetes occurred in 81% of patients receiving LENVIMA with everolimus, including 4% of patients. Diabetes was the most frequent cause of dose interruption and diabetes required dose reduction.
In patients receiving LENVIMA with pembrolizumab, the most common adverse reactions observed in LENVIMA-treated patients (>30%) were hypertension, increased blood pressure diastolic, macular rash, maculo-papular rash, generalized rash, rash, pruritus, paronychia, increased alkaline phosphatase, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), hypokalemia, and decreased sodium.

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 observed in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions observed in LENVIMA-treated patients (≥30%) were hypertension, increased blood pressure diastolic, macular rash, maculo-papular rash, generalized rash, rash, pruritus, paronychia, increased alkaline phosphatase, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), hypokalemia, and decreased sodium.

Table 3: Adverse Reactions Occurring in Patients with a Between-Group Difference of ≥5% in All Grades or ≥2% in Grades 3 and 4 in SELECT (DT)

**Vascular**
- Hypertension
- Headache
- Thrombosis
- Hypotension

**Gastrointestinal**
- Nausea
- Abdominal pain
- Constipation
- Diarrhea
- Oropharyngeal pain

**Metabolism and Nutrition**
- Decreased appetite
- Decreased weight

**Respiratory and Urinary**
- Proteinuria

**Skin and Subcutaneous Tissue**
- Palmar-plantar erythrodysesthesia

**Laboratory Abnormalities**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n=129 to 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>13 15</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>12 15</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>2 0</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>2 0</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>25 25</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>25 25</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>29 29</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>17 17</td>
</tr>
<tr>
<td><strong>Oropharyngeal pain</strong></td>
<td>17 17</td>
</tr>
</tbody>
</table>

**Laboratory Abnormalities**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 24 mg N=260</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>2 15</td>
<td></td>
</tr>
<tr>
<td><strong>Hypomagnesemia</strong></td>
<td>1 0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>3 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperbilirubinemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td><strong>Hypomagnesemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperbilirubinemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperbilirubinemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>1 0</td>
<td></td>
</tr>
</tbody>
</table>

**Hematology**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 24 mg N=260</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutropenia</strong></td>
<td>5 5</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>5 5</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>5 5</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>5 5</td>
<td></td>
</tr>
</tbody>
</table>

**Serious Including Fatal Hemorrhagic Events**

- Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure systolic.
- Includes paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
- Includes macular rash, maculo-papular rash, and rash.
- Includes paronychia, oral pain, paronychia, paronychia, palmar-sweat, tooth abscess, and toothache.

**Laboratory Abnormalities**

- Includes hypertension, paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
- Includes macular rash, musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes paronychia, oral pain, paronychia, paronychia, palmar-sweat, tooth abscess, and toothache.

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- Includes hypertension, paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
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- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
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- Includes hypertension, paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
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- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
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- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes paronychia, oral pain, paronychia, paronychia, palmar-sweat, tooth abscess, and toothache.

**Laboratory Abnormalities**

- Includes hypertension, paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
- Includes macular rash, musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes paronychia, oral pain, paronychia, paronychia, palmar-sweat, tooth abscess, and toothache.

**Laboratory Abnormalities**

- Includes hypertension, paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
- Includes macular rash, musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes paronychia, oral pain, paronychia, paronychia, palmar-sweat, tooth abscess, and toothache.

**Laboratory Abnormalities**

- Includes hypertension, paronychia, increased alkaline phosphatase, and increased aspartate aminotransferase (AST).
- Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal ulcer.
- Includes macular rash, musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes oral pain, glossodynia, and oropharyngeal pain.
- Includes nausea, vomiting, anorexia, and hypokalemia.
- Includes paronychia, oral pain, paronychia, paronychia, palmar-sweat, tooth abscess, and toothache.
≥20% of patients treated with LENVIMA and pembrolizumab in CLEAR. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), arthralgia, multiple myeloma, myeloid metaplasia, myelodysplasia, myelodysplastic syndrome, myasthenic syndrome, mycosis, nephrosis, nephritis, rupture and subarachnoid hemorrhage. Serious adverse reactions occurred in 51% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in <2% of patients were hemorrhage (9%), diabetes (2%), hypoglycemia, hyperglycemia, increased blood pressure, acute kidney injury (2%), adrenal insufficiency (2%), and pneumonia (2%).

Permanent discontinuation of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 77% of patients; 75% LENVIMA only, 80% pembrolizumab only, and 100% both drugs. The most common adverse reactions (≥2%) leading to permanent discontinuation of LENVIMA, pembrolizumab, or both were pneumonia (7%), myelodysplastic syndrome (3%), myocardial infarction (3%), hepatocellular injury (3%), acute kidney injury (3%), and diarrhea (2%).

Dose interruptions of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with pembrolizumab. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients receiving LENVIMA in combination with pembrolizumab. LENVIMA was interrupted in 73% of patients; 26% LENVIMA only, 29% pembrolizumab only, and 13% both drugs. The most common adverse reactions (≥2%) leading to permanent discontinuation of LENVIMA, pembrolizumab, or both were pneumonia (7%), myelodysplastic syndrome (3%), myocardial infarction (3%), hepatocellular injury (3%), acute kidney injury (3%), and diarrhea (2%).

Table 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in ≥20% of patients treated with LENVIMA and pembrolizumab in CLEAR.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>83</td>
<td>9</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68</td>
<td>10</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>43</td>
<td>2</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>3</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>25</td>
<td>3</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
<td>3</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>3</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>56</td>
<td>4</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>57</td>
<td>2</td>
<td>33</td>
<td>1</td>
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<tr>
<td>Venous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>56</td>
<td>29</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>27</td>
<td>5</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>3</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
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<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>5</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia syndrome</td>
<td>29</td>
<td>4</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal dysfunctions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urological dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyuria</td>
<td>30</td>
<td>8</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>21</td>
<td>5</td>
<td>16</td>
<td>2</td>
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<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>30</td>
<td>8</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Hepatobiliary dysfunctions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>30</td>
<td>8</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Nervous system

| Headache         | 23            | 1             | 16            | 1             |
| Peripheral edema | 42            | 2             | 12            | 0             |
| Sensory disorders|               |               |               |               |
| Headache         | 23            | 1             | 16            | 1             |

| Does not include any adverse reactions (≥2%) that occurred in patients receiving LENVIMA/pembrolizumab |               |               |               |               |
| Clinically relevant adverse reactions (≥20%) that occurred in patients receiving LENVIMA/pembrolizumab were myocardial infarction (1%) and angina pectoris (1%).

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>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>80</td>
<td>15</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64</td>
<td>5</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>61</td>
<td>34</td>
<td>59</td>
<td>28</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>59</td>
<td>17</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>58</td>
<td>7</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>57</td>
<td>8</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>55</td>
<td>7</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Increased serum amylase (ALT)</td>
<td>54</td>
<td>7</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>44</td>
<td>4</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Hypoammonemia</td>
<td>44</td>
<td>4</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>43</td>
<td>6</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>34</td>
<td>8</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>32</td>
<td>4</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>29</td>
<td>7</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>25</td>
<td>2</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Increased creatine x phosphocreatine</td>
<td>25</td>
<td>2</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

Hematology

| Hyponatremia | 54        | 9             | 54            | 9             |
| Thrombocytopenia | 29      | 2             | 27            | 2             |
| Anemia        | 26        | 3             | 24            | 3             |
| Leukopenia    | 24        | 2             | 22            | 2             |
| Neutropenia   | 21        | 1             | 20            | 1             |

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 10 mg N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</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>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia/Gastro-esophageal reflux</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Pain syndrome</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>
REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were fatigue, encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events.

The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of frequency, fatigue, diarrhea, hypertension, and mouth ulceration.

28% were White and 70% were Asian.

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions (≥5%) resulting in treatment discontinuation of LENVIMA were fatigue (5%), decreased appetite (4%), diarrhea (3%), proteinuria (3%), hypertension (3%), and palmar-plantar erythrodysesthesia syndrome (2%).

In Table 9, Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

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

In Table 11, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

In Table 12, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Endometrial Carcinoma

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

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).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and pembrolizumab, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, low gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 20% of these patients receiving LENVIMA and pembrolizumab. Serious adverse reactions with frequency ≥3% were hypertension (4.5%), and urinary tract infection (3.2%).

Discontinuation of LENVIMA due to an adverse reaction occurred in 28% of these patients. The most common (≥1 %) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1%), 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 reaction resulting in dose reduction of LENVIMA were hypertension (11%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthma (5%), and weight decreased (5%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (≥5%) adverse reaction leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (≥5%) adverse reaction leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (8%), decreased appetite (5%), vomiting (5%), increased alanine aminotransferase (5%), fatigue (5%), nausea (5%), abdominal pain (2%), weight decreased (2%), urinary tract infection (2%), increased aspartate aminotransferase (2%), asthma (2%), 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</th>
<th>Pembrolizumab 200 mg combination with LENVIMA N=342</th>
<th>Pembrolizumab 200 mg as monotherapy N=535</th>
<th>Pembrolizumab 200 mg in combination with LENVIMA N=342</th>
<th>Pembrolizumab 200 mg as monotherapy N=535</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Carcinoma (not MSI-H or dMMR)</td>
<td><strong>Adverse Reaction</strong></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Adverse Reaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67</td>
<td>0.9</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;c&lt;/sup&gt;</td>
<td>67</td>
<td>36</td>
<td>6</td>
<td>2.5</td>
</tr>
<tr>
<td>Hemorrhagic events&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25</td>
<td>6</td>
<td>15</td>
<td>0.8</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;c&lt;/sup&gt;</td>
<td>58</td>
<td>11</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58</td>
<td>8</td>
<td>20</td>
<td>2.9</td>
</tr>
<tr>
<td>Vomiting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37</td>
<td>2.3</td>
<td>21</td>
<td>2.2</td>
</tr>
<tr>
<td>Steatorrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35</td>
<td>2.6</td>
<td>26</td>
<td>1.2</td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34</td>
<td>2.6</td>
<td>21</td>
<td>1.2</td>
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<tr>
<td>Constipation</td>
<td>27</td>
<td>0</td>
<td>25</td>
<td>0.8</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal disorders&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>5</td>
<td>27</td>
<td>0.6</td>
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<tr>
<td>Metabolism</td>
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<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>7</td>
<td>21</td>
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<td>Investigations</td>
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<td>Decreased weight</td>
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<td>10</td>
<td>6</td>
<td>0.3</td>
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<tr>
<td>Renal and Urinary</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29</td>
<td>6</td>
<td>3.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Infections</td>
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</tr>
<tr>
<td>Urinary tract infection</td>
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<td>5</td>
<td>13</td>
<td>1.2</td>
</tr>
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<td>Nervous System</td>
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<td>Headache</td>
<td>26</td>
<td>0.6</td>
<td>9</td>
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<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>0</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
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</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23</td>
<td>2.9</td>
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<tr>
<td>Rash&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20</td>
<td>2.3</td>
<td>4.9</td>
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</tr>
</tbody>
</table>

<sup>a</sup> Graded per NCI CTCAE v4.03

### Table 12: Laboratory Abnormalities Worsened from Baseline<sup>c</sup> 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>Pembrolizumab 200 mg combination with LENVIMA N=342</th>
<th>Pembrolizumab 200 mg as monotherapy N=535</th>
<th>Pembrolizumab 200 mg in combination with LENVIMA N=342</th>
<th>Pembrolizumab 200 mg as monotherapy N=535</th>
</tr>
</thead>
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<tr>
<td><strong>Laboratory Test</strong></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
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<tr>
<td>Chemistry</td>
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<td>Basophils&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Monocytes&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>3</td>
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<tr>
<td>Direct bilirubin&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>18</td>
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<td>2</td>
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<td>15</td>
<td>2</td>
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<td>2</td>
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<td>2</td>
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<td>Total bilirubin&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Direct bilirubin&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Cholesterol&lt;sup&gt;c&lt;/sup&gt;</td>
<td>26</td>
<td>4</td>
<td>15</td>
<td>2</td>
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</tbody>
</table>
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 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Of the 62 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 elderly patients and younger patients.

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 RCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease.

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

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

OVERDOSAGE Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.

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Case-Based Roundtable Meetings Spotlight

surprises there. [There was] no increased toxicity in patients older than 65, something for our population [that is] always very important. And for patients that started to develop that peripheral edema, of course, [that toxicity was managed] with some diuretics.

Some practical information: It’s a 30-minute IV infusion. You start again every 3 weeks [and] you start with a higher dose. Subsequently, you step down to a lower dose. And it is recommended to give premedication, [in other words] steroids. [The prescribing information has] a nice algorithm or recommendation when it comes to decreasing the dose if you face severe cytopenias, which, again, seem to be the most commonly seen adverse events.

**What is new and upcoming when it comes to lonca-T?**

You have phase 3 trials trying to look at lonca-T plus rituximab vs R-GemOx [eg, LOTIS 5 (NCT04384484)] because again, in their calculation, R-GemOx is still a treatment that is very commonly used for DLBCL. And I think they are right; it’s something that is relatively easy to use and most of us are going to feel comfortable using R-GemOx, so they’re just trying to prove that lonca-T plus rituximab is better than R-GemOx. They’re going to have a part 1...a run-in initial part of the therapy that is going to be the evaluation of lonca-T plus rituximab. Again, it has not been done before so they need to do it that way. If they prove that lonca-T plus rituximab is safe, then you come in with part 2, which is...the randomization of lonca-T plus rituximab vs R-GemOx and a decent number of patients north of 300.

**Multiple participants voted for tafasitamab (Monjuvi) plus lenalidomide (Revlimid). What is the background for using this combination?**

[This combination is approved for use in patients with DLBCL not always specified or DLBCL arising from a low-grade lymphoma, who are not eligible for an autologous stem cell transplant.] Lenalidomide [acts as an] immunomodulator, [an anti-CD19 monoclonal antibody]. It has activity in many diseases, [such as] myelodysplastic syndrome, multiple myeloma, and mantle cell lymphoma, so it’s not surprising that it has activity in DLBCL. The name of the trial that led to the approval was called L-MIND [NCT02399085], and it’s a phase 2 study.

They were looking for patients that had received 1 to 3 prior lines of therapy...not eligible for high-dose chemotherapy and autologous stem cell transplant, and, just as [with] lonca-T, you start a little bit more aggressively. In cycle 1 to cycle 3 you have more infusions of tafasitamab. In cycle 4 to cycle 12, [you have the] same dose but you’re going to give it less frequently, only 2 infusions per month. Lenalidomide is a 25-mg/day dose. [From] day 1 to 21, sometimes, the higher the dose of lenalidomide the tougher the disease [can be] to tolerate. It is not a completely clean drug either. You have patients that can complain of skin rashes [and] diarrhea, [and] there’s a chance of having a clot, so that’s why I usually like to prescribe some sort of antithrombotic prophylaxis. I usually go with a baby aspirin [for] my patients [to whom] I prescribe lenalidomide.

Tumor flare is also something that has been described. When I put patients on lenalidomide, sometimes they call me saying, “What you gave me did not work.” The lymph node is just growing and growing quickly, and I tell them to come to the clinic. By the time they come to the clinic, the mass has receded; it just went away. It happens usually at the very beginning when you start lenalidomide and it’s called tumor flare. The lymphoma starts fighting that lenalidomide and that causes a little bit of worsening lymphadenopathy, but if you muscle through, the lymph node shrinks in size again.

And then if you face stable disease or higher, CR or PR, you can continue the tafasitamab without lenalidomide until progression, cycle 12 or more, and the primary end point in the trial was ORR. One of the things I always

—JAVIER L. MUNOZ, MD, MBA

continued from page 6
Describe the results from the L-MIND trial.

The ORR—again, the one I care about the most—would be the longest follow-up. In this case, more than 35 months after [treatment with] tafasitamab/lenalidomide, there was a 57.5% ORR. I care about the CR, which was 40%, and a median duration of response of 43.9 months, so [this is] really high for a maneuver that is not CAR T-cell based and you do not necessarily have to send the patient to another oncology center.

At a median follow-up of 33.9 months, the median progression-free survival is 11.6 months. So again, [this therapy is] not for everyone; you could prescribe it and [see] if there is progression of disease. Then, of course, we could still be happy to see your patients if you consider CAR T cells, but for the ones that do go into CR, they seem to have good options there. The median overall survival at a median of 42.7 months follow-up was 35.5 months.

If it is a safe drug, you’re not going to have a lot of people stopping it or discontinuing treatment because of the severe adverse events. Twelve percent stopped treatment due to toxicity, due to adverse events, and serious adverse events did occur in 51% of patients, so again, it’s not like drinking a glass of water. Treatment-emergent adverse events leading to death [were observed in] 13%, or 4 of 30 patients. There were patients with dose reductions; 45.7%...had at least 1 or more events of dose reduction, particularly of the lenalidomide. [There were some] grade 4 toxicities, such as neutropenia. If you look at tafasitamab monotherapy, you still see neutropenia, but definitely, with the addition of lenalidomide, [it is] higher all across the board when it comes to toxicity. So it seems that the combination of tafasitamab/lenalidomide gives you more efficacy but it also gives you a little more toxicity.

What is the manufacturer of tafasitamab doing when it comes to future trials?

[There is the RE-MIND trial (NCT04150328), which is] looking at real-world data. [Investigators are evaluating] tafasitamab plus lenalidomide vs lenalidomide in transplant- ineligible patients with relapsed/refractory DLBCL, and the primary end point is ORR. If I had to choose or guess, tafasitamab/lenalidomide is going to do way better than lenalidomide monotherapy per se. I would only choose lenalidomide monotherapy in patients with DLBCL that have the activated B-cell [ABC] subtype instead of the germinal center subtype.

There are some data showing that [patients with] ABC seem to respond a little bit better to lenalidomide or even ibrutinib [Imbruvica]. Ibrutinib is not approved in DLBCL, but in clinical trials we have seen that the ABC subtype seems to work a little bit more when you expose those patients to Bruton tyrosine kinase inhibitors, compared with germinal center DLBCL.

Polatuzumab vedotin (Polivy) plus or minus bendamustine and rituximab (pola-BR) had the most votes in the earlier poll. What role does that regimen play in DLBCL?

This particular study [NCT02257567] was for DLBCL, but there was a cohort that also had follicular lymphoma. [The investigators] thought, in their calculation, that it was going to be a home run for follicular lymphoma and they were not sure about DLBCL. The numbers ended up looking better for DLBCL than follicular lymphoma, and that is why it’s not approved right now in follicular lymphoma. It’s approved in DLBCL.

When it comes to the cohort for DLBCL—80 patients, bendamustine vs pola-BR—forget a little bit about the follicular lymphoma cohort because it was negative. It is not FDA approved in follicular lymphoma at this point and you have the exclusion criteria there. Prior allogeneic stem cell transplant was excluded, transformation of indolent disease to DLBCL was excluded, [and grade 2 or higher] neuropathy was excluded. The payload in polatuzumab is a vinca alkaloid. It causes neuropathy so it makes sense that you would be careful to include those patients.

In the pola-BR arm, the oldest age of patients enrolled was 86; in the bendamustine arm the oldest age was 84 years. These were patients that had high IPI scores in [the pola-BR] arm, 55%, but in the bendamustine arm [it was] 72.5%, again highlighting the differences. It seems that patients in the bendamustine arm had higher IPI scores [than] the patients in the pola-BR arm, so that’s a difference that I identified.

The median prior lines of therapy was 2 for both, so I think that was fair. Refractory [disease was], numerically, a little bit higher with bendamustine and rituximab. Prior stem cell transplant [numbers were] a little bit higher with pola-BR. So, if you truly want to be the devil’s advocate, you could say you were selecting a little...
bit for tougher patients in the bendamustine and rituximab arm because there were patients with numerically higher refractory disease and numerically higher IPI in that particular cohort. Also, if more patients had received prior stem cell transplant in the pola-BR arm, maybe they had a better protoplasm or a better phenotype compared with the other arm. But those numbers are numerically different but not dramatically different. Finally, there was a little bit more germinal center DLBCL in the bendamustine [vs the] rituximab arm, 42% vs 37%, [respectively].

How did patients respond to pola-BR in this trial?
The ORR was 45% for pola-BR, and you could see that for bendamustine and rituximab it was only 17.5%. The CR rate was 40%, so a reasonable number of patients achieved CR with polatuzumab; 40% is a good number. Remember what you get with CAR T cells—40% to 50%, depending on the construct.

[Regarding] progression-free survival, the median for pola-BR was 9.5 months vs 3.7 months if you only go with bendamustine and rituximab. Again, it’s not for everyone. It’s not necessarily a home run and probably not a destination therapy; it’s probably a breach, but you could get several months for your patient when it comes to putting them in remission—9.5 months. The overall survival had differences there, too, [approximately] a year. The overall survival was 2.4 months for pola-BR vs 4.7 months for bendamustine and rituximab.

Let’s take a look at the peripheral neuropathy: grade 3 or 4 was 0%, so that is good, but 43.6% had some degree of neuropathy so that will be grades 1 to 2. Forty-three percent is almost as high as the percentage of patients who achieved CR, which was 40%. Approximately 40% of patients will also develop peripheral neuropathy. When it comes to bendamustine and rituximab, not surprisingly, the number is way lower—7%. Neuropathy is not 1 of the most common things that you see with bendamustine and rituximab.
LUNG CANCER

Roundtable Discussion: Herbst and Sabari Discuss Practice Updates for Patients With Metastatic Lung Adenocarcinoma

CASE SUMMARY

A 72-year-old White man presented with chest pain, cough, and dyspnea and had type 1 diabetes but was a former smoker with 10 pack years. A CT of the chest and abdomen showed a 9-cm spiculated mass in the left lower lobe, loculated pleural effusion in the left hemithorax, diffuse liver lesions, and a right adrenal metastasis. Further PET/CT scan showed an 18F-FDG uptake in the left lung mass, pleura, liver lesions, and a right adrenal gland nodule. A brain MRI showed a solitary brain lesion of 2 cm, and a physical exam was notable for decreased breath sounds in the left lung base, but no hepatomegaly, and an ECOG performance score of 1. Lab work was unremarkable, but image-guided biopsy of the liver lesion showed a poorly differentiated adenocarcinoma of the lung with a PD-L1 tumor proportion (TPS) of 95%.

DISCUSSION QUESTIONS

• What type of molecular testing would you obtain for a patient such as this one?
• Are you using liquid biopsies up front?

STRAUSS: I’d probably check next-generation sequencing [NGS] on tumor tissue, and then I might do it on blood as well. I’ve been doing blood and tumor tissue together.

GILLANI: We do the same thing now, and we have moved away from à la carte testing and try to do up-front tissue-based NGS as well as liquid DNA-based [testing].

NEWSOME: I would generally start with tissue testing first; if that gave me the information I needed, I wouldn’t necessarily do a liquid biopsy up front. If [the tissue testing] didn’t give me the information I needed or if there were not enough tissue, then I would typically use a liquid biopsy.

VIVEKANANDARAJAH: I typically do NGS on the tissue, and I send for the liquid biopsy at the same time.

SABARI: In all patients, even patients with squamous cell carcinoma, I obtain tissue-based NGS up front. We do have an RNA-based assay, as well as a DNA-based assay.

HERBST: I would do an NGS profile [as well]. There are 7 or 8 different actionable mutations that you wouldn’t want to miss here, and [to] give them the best care, you would want to get them all. Liquid biopsy
can also help, if you can add that, but [whether you do] it up front or not it depends [on if] it’s paid for or not. If you can get it paid for, it doesn’t hurt. But you can also wait.

For nonsquamous non–small cell lung cancer [NSCLC], the National Comprehensive Care Network [NCCN] recommends frontline molecular testing for MET exon 14 skipping and for mutations in EGFR, ALK, ROS1, BRAF, NTRK1/2/3, RET, and now KRAS. This is hot off the NCCN press because of the new Amgen drug, sotorasib [Lumakras].

This testing should be conducted as part of a broader molecular testing regimen and [should include] PD-L1 testing, of course. A broad molecular panel–based NGS approach is recommended because it minimizes tissue use and potential wastage, identifies rare driver mutations, and it’s the way to improve patient care.

If there is insufficient tissue to allow for all this testing, [such as with a] repeat biopsy, plasma testing, or both should be done. Although PD-L1 expression can be elevated in patients with an oncogenic driver, the targeted therapy for the oncogenic driver should take precedence over treatment with an immune checkpoint inhibitor [ICI], [according to these NCCN guidelines].

What that’s saying is that if PD-L1 expression is high and there is an EGFR, ALK, or ROS1 [mutation in the tumor], it’s probably the mutational status that’s driving PD-L1 expression. The recommendation, and I would agree, would be to use the targeted therapy first.

SABARI: Back in 2016 and 2017 when we were really excited about immunotherapy, we used to try to use it in the frontline setting. However, I think the rate of immune-related adverse events is quite high in patients who receive up-front PD-L1 inhibitors followed by tyrosine kinase inhibitors.

We know from retrospective studies, as well as some prospective studies, that the response rates and the durability of response [are] low. So I would really avoid using a PD-1 or PD-L1 inhibitor in the driver-mutant population.

GILLANI: Is this [testing] stage dependent, or does it happen automatically? [That is], do you have to tell your pathologist that [a given patient] is stage IV or has unresectable stage III disease? Or are you doing it in all patients, including earlier-stage patients?

NEWSOME: [Given] the data on adjuvant EGFR inhibitors, I’m generally doing it up front, no matter what stage the [patient is], as opposed to waiting until [the patient] develops metastatic disease. We usually have to tell our pathologists what we want, and that’s how we’re doing it.

VIVEKANANDARAJAH: I agree, especially in patients who are nonsmokers, I’m doing the EGFR testing up front but just in the adjuvant setting.

CASE UPDATE

- Molecular testing:
  - NGS: negative for molecular aberrations in EGFR, ROS1, BRAF, ALK, RET, MET, ERBB2, NTRK, and KRAS
  - Microsatellite stable

DISCUSSION QUESTION

- What would be your preferred therapy for this patient?

SABARI: I’m in the minority here. Given the PD-L1 expression of 95%, I would spare this gentleman chemotherapy in the front line. I would give a single-agent PD-1 inhibitor, and this is based on the KEYNOTE-024 data [NCT02142738] from 2016. I’m curious [about] why others would do platinum-doublet chemotherapy plus therapy that targets [either PD-1 or PD-L1]. Is it the bulk of disease? The symptoms?

VIVEKANANDARAJAH: I [would use] the platinum doublet with anti–PD-L1 therapy because of the bulky disease. Also, I am not sure about the patient’s age, but I thought it was relatively young, and with the amount of disease burden that was there, I thought it [would be] better to use the chemotherapy option with the anti–PD-L1 therapy.

ASIK: I [would use] single-agent PD-L1 therapy (pembrolizumab [Keytruda]), based on the 95% PD-L1 [expression].

HUANG: I also [would use] single-agent pembrolizumab.

NEWSOME: I have to say that I [am] torn between using a single-agent PD-1– or PD-L1–targeted therapy versus combining that with platinum-doublet chemotherapy. This is a situation where you need to see the patient. You have to have a conversation with the patient. These decisions are not always made in isolation. I think [for this patient] I [would use] chemotherapy with PD-L1–targeted therapy because he did have a fair bulk of disease, he was relatively young, and there was a 2-cm brain metastasis.

I guess the question is, what do we do with the brain metastasis? I know that immunotherapy does achieve central nervous system penetration, but pemetrexed [Alimta], which presumably is what people would use [in the chemotherapy option], gets decent penetration as well.
That is what pushed me [toward adding] the chemotherapy doublet. But again, I was torn between the single-agent [immunotherapy] and the chemoimmunotherapy.

HERBST: A 2-cm metastasis is a little bit bigger than I’d be comfortable with just watching, I probably would have used a gamma knife or something, but [you make a] good point there.

The NCCN guidelines offer several first-line therapy choices for patients with adenocarcinoma and PD-L1 expression of at least 50%. There’s pembrolizumab, pembrolizumab plus chemotherapy; atezolizumab [Tecentriq], now licensed in this setting based on [data from the] IMpower110 trial [NCT02409342]; and cemiplimab-rwlc [Libtayo], [a new drug] supported by category 1 data.

We also have the quadruplet regimen that consists of carboplatin, paclitaxel, bevacizumab [Avastin], and atezolizumab; the combination of carboplatin, albumin-bound paclitaxel [Abraxane], and atezolizumab; and the combination of ipilimumab [Yervoy], nivolumab [Opdivo], and pembrolizumab, [and either carboplatin or cisplatin].

There’s a lot of choices here. I think that I would probably go with a single-agent drug, and atezolizumab, cemiplimab, or pembrolizumab are all reasonable.

SABARI: I would do single-agent pembrolizumab here, but is there any rationale behind using one PD-1 or PD-L1 inhibitor versus another in the single-agent setting and with PD-L1 expression greater than 50%? [These inhibitors] all have NCCN category 1 data.

HERBST: No, I think it’s a matter of choice. These drugs have not been compared head-to-head; they’ve all been compared with chemotherapy, but I think these drugs are all quite equivalent.

SABARI: One thing I have found is that the quadruplet regimen of carboplatin, paclitaxel, bevacizumab, and atezolizumab is a lot tougher to tolerate than single-agent therapy. And the CheckMate 9LA regimen [NCT03215706], ipilimumab, nivolumab, and chemotherapy, is a lot harder to tolerate than single-agent PD-1-targeted therapy.

I do think there is a role for those combinations if you have a younger patient with bulky disease if you want to [treat aggressively], but I agree with using single-agent pembrolizumab in the front line most of the time.

GILLANI: How much more response do you [achieve with] chemoimmunotherapy versus with immunotherapy alone in a patient like this with high PD-L1 expression?

This is a 70-year-old man, [so] we might have one shot at the goal, and if we don’t get a response out of single-agent immunotherapy, we could be in trouble.

HERBST: The response with a PD-1- or PD-L1-targeting agent used alone is upward of 40%. The chemotherapy probably increases that a little bit but with much more [adverse] effects. The question of what [happens] if you add the chemotherapy if you don’t have response [to the single agent] is being studied right now in a trial that’s being done [by the] SWOG [Southwest Oncology Group] Cancer Research Network.

DISCUSSION QUESTIONS

- What are the systemic therapy options for this patient?
- What factors influence your decision to use ICI monotherapy over chemotherapy plus ICI therapy for metastatic NSCLC with high PD-L1 expression?

ASIK: I would use a single-agent PD-L1 inhibitor because of the high PD-L1 expression, 95%. And again, pembrolizumab covers the brain metastasis too. That’s my reasoning.

BRAUNSTEIN: I [would choose] the platinum doublet with the PD-L1 inhibitor. In the KEYNOTE-189 trial [NCT02578680], I think that there was no real survival benefit as the responses looked better [in patients like this one who had a] higher [PD-L1] TPS [tumor proportion score]. Just given the extent of this patient’s disease I think adding chemotherapy would be a benefit.

MALIK: I [would choose] the combination because there are widespread metastases, including in the brain. [I also agree] that I may have one shot at this in the beginning, and if the performance status decreases, I may not be able to introduce chemotherapy in a reasonable fashion later.

STRAUSS: I’ve been burned a couple times when giving immuno-oncology monotherapy to patients with high PD-L1 expression, so I feel like it protects you to give something with a little bit of a higher response rate, [which acts] as a backup in case the PD-L1 agent doesn’t work.
HERBST: I think that I would try the single agent and then add chemotherapy if [the single agent] didn’t work, but again, you really need to see the patient.

CASE UPDATE
The patient is strongly opposed to chemotherapy and opts for a single-agent ICI.

DISCUSSION QUESTION
Which ICI are you most likely to recommend for this patient: atezolizumab, cemiplimab, pembrolizumab, or something else?

HERBST: These drugs are probably equivalent, but most of the data [support] pembrolizumab; that’s why the market is pretty much cornered by pembrolizumab, as I think it should be. The 5-year data from the KEYNOTE-024 trial showed 35% survival. When I was doing this in 1993, in frontline lung cancer, [survival at] 5 years was 0%, and [survival at even] 2 years was almost 0% in the metastatic setting.

Has anyone here had their pharmacy suggest that they use something else for cost reasons? Has anyone ever tried anything else in the frontline setting? Or is pembrolizumab just a reflexive choice?

BRAUNSTEIN: Yes, [it is] somewhat reflexive, just based on the KEYNOTE-024 study. To some extent, I feel like [these drugs are] interchangeable, but I typically use pembrolizumab.

MODI: We typically use pembrolizumab. It’s [the] way to go if the TPS for PD-L1 is more than 50%.

GILLANI: Yes, I use pembrolizumab too, but we have got a very aggressive cemiplimab pharmaceutical representative who reminds me almost every week to consider using this drug and who sends me the information from the NCCN guidelines and The Lancet paper.

HUANG: Yes, we have long-term data for pembrolizumab; we have been using this [drug] for a long time. You can use it every 3 weeks or every 6 weeks. I don’t know why we’d change to something else. I use this a lot already. I’m very familiar with this drug.

NEWSOME: I use pembrolizumab mostly for [the reason that was just mentioned]—the option to go every 6 weeks. I don’t usually start giving it every 6 weeks; I start giving it every 3 weeks, but [later] you have the option to [space the doses] every 6 weeks, and the patients are having good response and tolerating it.

BRAUNSTEIN: I [agree with] what everybody has said so far: the dosing schedule and the efficacy. I tend to use pembrolizumab more in the nonsquamous NSCLC.

SABARI: So site, burden of disease, and burden of metastasis [are common reasons for] adding chemotherapy.
Does the burden of metastasis or site of disease help guide the [choice of a] PD-1 or PD-L1 inhibitor?

HUANG: Yes, if patient has a lot of tumor burden and is symptomatic, I will look for whatever combination will produce the highest response rate.

[For example], atezolizumab, bevacizumab, pemetrexed, and carboplatin together produced an approximately 60% response rate.16

MODI: Usually I prefer the schedule of every 3 or 4 weeks, and we continue until disease progression.

TANG: I have a patient on single-agent pembrolizumab, and the patient now shows no disease. I will continue the single agent until the disease progresses. She [is now] 2 years out. I guess if she hits 5 years, [I might have] a discussion [with her about discontinuation], but for now I will continue to give her the single-agent treatment.

ASIK: I continue for 2 years if there’s no progression. I prefer pembrolizumab administered every 6 weeks.

ZHU: I would continue until disease progression if the patient can tolerate it.

HUANG: I usually do it for 2 years, but I will do a PET [positron emission tomography] scan. If there is still residual disease, I continue. If the PET scan is negative, I stop there.

STRAUSS: I think that the patient preference comes into play here. Some patients are very against stopping it; it’s kept them alive beyond [what they expected], so they’re hesitant to stop. But then again, some patients are happy to stop and be free of it. So I think patient preference is important in this discussion.

HUANG: I would change to chemotherapy. If a patient does not have much response [and has] progression with initial treatment, I would not continue. I would stop [the ICI] and just switch to chemotherapy. If a patient has a very good response for a while and then progresses, I might add chemotherapy [to the ICI].

MALIK: If there is disease progression, I would change the treatment. I don’t have your kind of experience with pembrolizumab or the other agents, so I’m not aware of [any] benefit of continued treatment during disease progression.

DISCUSSION QUESTIONS

- The administration scheduling options vary for each agent. How do these align with your schedule for patient follow-up and monitoring?
- How long do you continue single-agent ICI?
- Is there a point at which you would discuss discontinuation with your patients?

HERBST: This patient never really benefited that much to begin with, correct?

SABARI: Yes. I would stop the immunotherapy here, in this setting, and I would generally transition to chemotherapy. To Dr Huang’s point, though, if a patient has benefited on [ICI] therapy for a prolonged period (12 months or so), I generally do add chemotherapy [to the ICI]. I think there is an ECOG [Eastern Cooperative Oncology Group] study looking at this question.

HERBST: Right, the INSIGNA trial [NCT03793179]. [In this trial, patients] start with single-agent [pembrolizumab] and then switch to chemotherapy alone or to chemotherapy plus pembrolizumab17 because we don’t know if you should keep [the pembrolizumab] going.

CASE UPDATE

- When the patient returns for cycle 4, he reports worsening back pain and shortness of breath.
- CT scan shows progression in the primary tumor and growth of an adrenal metastasis.

DISCUSSION QUESTIONS

- Would you change treatment in this patient?
- Do you ever treat beyond progression? If so, when? For this patient: atezolizumab, cemiplimab, pembrolizumab, or something else?

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FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM
BLENREP is the first and only BCMA-targeted ADC monotherapy. So you can offer your RRMM patients a different option.

INDICATION
BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on 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

WARNING: OCULAR TOXICITY
BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS.

ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; RRMM=relapsed or refractory multiple myeloma.

Learn more at BLENREPHCP.com
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

FORGE AHEAD

So you can offer your RRMM patients a different option.

BLENREP is the first and only BCMA-targeted ADC monotherapy.

IMPORTANT SAFETY INFORMATION

Ocular Toxicity: Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 6% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 2 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Advertise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

ADVERSE REACTIONS

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to a adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

Females and Males of Reproductive Potential: Based on findings in animal studies, BLENREP may impair fertility in females and males.

Geriatric Use: Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

Renal or Hepatic Impairment: The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
the median time to resolution was 2 months (range: 11 days to 8.3 months). For patients in whom events resolved, study withdrawal, or lost to follow up. For patients in whom events resolved, study withdrawal, or lost to follow up.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.1)].

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE
BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Ocular Toxicity
Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (70%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy
Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infectious keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 or 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 3% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes
A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction
Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1) of full Prescribing Information].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machines.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (6.2)].

5.2 BLENREP REMS
BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)].

Notable requirements of the BLENREP REMS include the following:
  a. Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
  b. Prescribers must be licensed in a state where BLENREP is available.
  c. Patients must be enrolled in the BLENREP REMS and comply with monitoring.
  d. Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.

Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENPREMS.com and 1-855-209-9188.

5.3 Thrombocytopenia
Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days.

Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.9%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients.

Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

5.4 Infusion-Related Reactions
Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)]. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Perform premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity
Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

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

  a. Ocular toxicity [see Warnings and Precautions (5.1)].
  b. Thrombocytopenia [see Warnings and Precautions (5.3)].
  c. Infusion-related reactions [see Warnings and Precautions (5.4)].

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma
The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 93). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

(continued on next page)
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (25%) and thrombocytopenia (9%).

The most common adverse reactions (>20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (>5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

Table 1. Adverse Reactions (>10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62 (21)</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49 (22)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32 (18)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57 (2)</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43 (4)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38 (3)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26 (1)</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22 (1)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20 (2)</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1). Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. 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 reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

(continued on next page)
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blm in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception

Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility

Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats [see Nonclinical Toxicology (13.1) of full Prescribing Information].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m² or end-stage renal disease [ESRD]) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

- Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia

- Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions

- Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].
- Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

- Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

Infertility

- Advise males and females of reproductive potential that BLENREP may impair fertility [see Use in Specific Populations (8.3)].

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BLMADV190001 January 2021

Produced in USA.
**Targeted Oncology™: What is the background and management of GVHD?**

**POPAT:** GVHD is the leading cause of nonrelapse mortality or treatment-related death following allogeneic transplant. We recently did a study of 200 patients with a new regimen, looked at the data, and found that at day 100, about 5% of the patients had treatment-related mortality. Most were related to organ damage.

At 3 months to 1 year, [which is the point that] many of you will see these patients in the community, we had 15% additional mortality. So we lost about 24 patients in that period—22 of 24 of whom had GVHD at some point during their disease course. Many of them died of GVHD, but some developed severe infection because they were so immunosuppressed because of GVHD and its treatment.

The treatment-related mortality of transplant is due to GVHD. We need to bring it down to make transplant as safe as possible. Unfortunately, a lot of [clinicians] see these patients in the community because typically at the transplant center, we see them up to day 100. So if the mortality due to GVHD is occurring after 3 months or 1 year, I think it behooves you [to] have some familiarity with this disease.

So we will talk about both acute GVHD [aGVHD], which traditionally was defined as GVHD occurring before 100 days, and chronic GVHD, defined as that occurring after 100 days. They are different syndromes that we think of as 2 different entities: one that occurs early and 1 that occurs late, but with different manifestations.

With standard prophylaxis, about 50% of the patients still develop GVHD, so this is still a significant problem. Of these, about half do not respond to treatment. In addition to steroids used as a first-line therapy, some of the other treatments have a big role. When we condition patients with chemotherapy and radiation therapy [during transplant], this damages the normal host tissue because it is a highly lethal treatment, even more than regular chemotherapy. At 2 to 3 times the normal dose, this will cause toxicity.

So there is tissue damage, which exposes the normal antigens on the patient recipient host tissue that then attracts the donor’s T cells. The donor’s T cells see the antigens that are presented by the recipient, known as antigen-presenting cells [APCs] to the donor immune system. Then you have the T-helper 1 lymphocyte cell response, resulting in the release of cytokines and effector cells, which damages normal host tissue and causes GVHD.

The typical target organs in aGVHD are 3: the skin, gastrointestinal tract [GIT], and liver. So you may see skin manifestations like maculopapular rash, lower GIT...
involvement like diarrhea, or nausea and vomiting, and liver abnormalities manifesting as elevated enzymes like alkaline phosphatase; but typically it is a cholestatic picture. For prevention, we typically try to suppress the donor’s immune system [by giving the recipient] cyclosporine and tacrolimus. These are called calcineurin inhibitors, and they inhibit the T cells. Methotrexate is the other agent that is used.

How does prophylaxis play a role in treating GVHD? Most places do GVHD prophylaxis with tacrolimus and methotrexate. Others used include mycophenolate mofetil, sirolimus, [a T-cell antibody using] antithymocyte globulin [ATG] and alemtuzumab, and ex vivo T-cell depletion [with CD34 selection]. But more commonly, many centers including ours are using posttransplant cyclophosphamide, which has changed the GVHD profile. So depending on where you are, patients will receive tacrolimus, methotrexate or posttransplant cyclophosphamide and tacrolimus and then [mycophenolate mofetil]. The APC activates the T cell, and anything that stops this interaction will result in reduction of GVHD. So the first thing that you could do is just get rid of the T cells through ex vivo T-cell depletion. In a lab, we can take out all the T cells and give only stem cells, and you get rid of GVHD—but you end up with a different problem. The alternative is you give antibodies like alemtuzumab or ATG, which reduce the T-cell numbers. There are some other agents that you could use too. You can suppress the cytokines, so you have drugs that inhibit the tumor necrosis factor receptor, such as etanercept [Enbrel] and infliximab [Remicade]. You could also use JAK [Janus kinase] inhibitors and inhibit multiple cytokines. Essentially, you can reduce the signaling that innervates the T cells.

Are there institutional preferences for grading, staging, or risk stratification of aGVHD? The stages [based on the Mount Sinai Acute GVHD International Consortium (MAGIC)] go from 0 to 4. The higher the stage, the greater the severity. If the skin area involvement is more than 50%, it is stage 3. But if you have bullae or erythroderma, it is stage 4 and very severe. The details are not important. What is important is the severity.

If you have a very high [bilirubin of more] than 15 mg/dL, then it becomes stage 4, and for GIT symptoms, if you get more than [1000 mL of diarrhea per day], then it is beyond stage 2 GVHD. So stage 4 being more severe has a very high mortality of 80% to 90.

They are now dividing patients into standard risk vs high risk based on severity. The problem is that if you have high-risk disease, the response rate to steroids is lower. For pure standard-risk disease, there is an almost 70% response, but if you have high-risk disease, it is only 40%. The patients with high-risk disease have a higher treatment-related mortality at 6 months [of 44%], whereas that of the standard-risk group is 22% [P < .001]. This translates into overall survival too.

You can classify GVHD based not only stage but on [a panel of 6] biomarkers. These are mostly in the specialized centers with interest in GVHD. Most centers do not even do this, but it is important from a GVHD research standpoint. The point here is that it differentiates those with high-risk and low-risk disease.

What is steroid-refractory GVHD, and how is it managed? This is GVHD in a patient who progresses after steroid administration of 2 mg/kg or greater for 3 to 5 days or anybody who fails to improve within 1 week of treatment initiation. When you think of GVHD, start treatment quickly. Likewise, when you think about steroid-refractory GVHD, start treatment early. Based on the NCCN [National Comprehensive Cancer Network] guidelines, there are multiple agents used for steroid-refractory GVHD including infliximab. Extracorporeal photopheresis can also be done. But on top of the list is ruxolitinib [Jakafi], which is an FDA-approved agent.

Together with agents for chronic GVHD, a total of 3 agents are approved. For chronic GVHD, belumosudil [Rezurock], initially known as KDO25, is a new one on the block, and ibrutinib [Imbruvica] is a drug we use for chronic lymphocytic leukemia too. GVHD is initiated by damage of the organ systems by the chemotherapy [that] drives the T cell or the donor immune system response, which is mediated by cytokines. One way to inhibit this reaction is by inhibiting cytokines at several levels and blocking the transmission of their signals. All cytokines use the signaling pathway called JAK kinase, STAT pathway, or JAK-STAT signaling pathway. These are the receptor tyrosine kinases, and when the cytokine is attached, it transmits the signal for their activation.

So, if you could block this pathway, you could reduce this reaction and reduce inflammation. Ruxolitinib is a drug that does that. You may have used it in myelofibrosis, where it causes a magical response.

I see a lot of patients with myelofibrosis who have a huge spleen, and they get ruxolitinib and the spleen goes down in size. In the studies, we saw that these patients started feeling better and started gaining weight because they had a drop in the cytokine levels. The first time we saw there was a reduction in the cytokine levels,
many of us wanted to study this drug for GVHD because we knew that cytokines played a big role in GVHD.

**What are the data behind using ruxolitinib in both acute and chronic GVHD?**

In the phase 2 REACH1 study [NCT02953678], they found a benefit. So it was then taken to the phase 3 REACH2 study [NCT02913261], where patients with steroid-refractory acute GVHD were randomized to receive ruxolitinib or best available therapy [selected by investigators before randomization]. The end points were overall response at day 28. So a very simple design.⁸

At day 28, ruxolitinib had a 62% response rate as opposed to the controls at 39% [odds ratio (OR), 2.64; 95% CI, 1.65-4.22; \( P < .001 \)], which was statistically significant. The durable overall response at day 56 for ruxolitinib was also higher at 40% vs 22% for the controls arm [OR, 2.38; 95% CI, 1.43-3.94; \( P < .001 \)]. Patients with all grades of GVHD responded to therapy.⁹

Patients who got ruxolitinib had a better duration of response, and those in the control arm lost the response to treatment earlier. All the affected organ systems responded, and you did not see downshifting of the organs. Mainly in acute GVHD, skin and lower GIT [had better responses]. This resulted in better median failure-free survival in ruxolitinib of 5 months vs 1 month for the control arm [HR, 0.46; 95% CI, 0.35-0.60].

Obviously, this is a drug that suppresses blood counts, so the incidence of thrombocytopenia was higher, which was also seen in some patients with myelofibrosis, and some anemia, although it was not seen in this study.⁹

**POLLING QUESTION**

During a live virtual event, Popat asked participants, “Considering the REACH2 trial data, what do you use as first-line therapy for steroid-refractory, acute graft-vs-host disease?”

<table>
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</tr>
<tr>
<td>Other</td>
<td>0%</td>
</tr>
</tbody>
</table>

**What do you feel is something community physicians think about when treating patients with GVHD?**

A take-home point from my standpoint for clinicians who work in the community, [the setting where] you are going to see the patient with aGVHD is...either if they are not controlled well at a university hospital or a referral center like ours and second, when we are tapering or reducing immunosuppression, particularly tacrolimus. So for a patient who has a recent change, drop, or stop in the immunosuppression agents and comes in with rash or diarrhea, think about GVHD.

Some of these patients also can have elevated transamases, which in fact is another common manifestation of this withdrawal.

**Point No. 2:** If you are thinking about GVHD and the patient is significantly sick, after calling your local transplant doctor, probably think about using steroids. Then of course, if the steroids fail, ruxolitinib is an option; but you can let your referring doctor decide whether they want to use it or not. But you can certainly mention to them that this is a good agent.

**REFERENCES**

Grisham Discusses Use of Multiple PARP Inhibitors in Treating Ovarian Cancer

CASE

March 2013

- A 49-year-old Black woman presented to her primary care physician complaining of abdominal bloating and nausea.
- Medical History: chronic hepatitis B virus infection, mild hypertension
- Family history: Mother died of breast cancer at age 59 years; cousin on mother’s side died of ovarian cancer at age 65 years.
- CT scan: ascites and bilateral 8-cm adnexal masses
- Cancer antigen 125 (CA125): 285 U/mL

- The patient underwent an exploratory laparotomy followed by omentectomy, a bilateral salpingo-oophorectomy, pelvic lymph node dissection, an appendectomy, and resection of pelvic nodules for stage IIIC high-grade serous carcinoma (HGSC).
- No gross residual disease (RO)
- Germline molecular testing: BRCA wild type, homologous combination deficiency (HRD)
- Pathology: high-grade serous epithelial ovarian cancer involving omentum, both ovaries, and 3 micrometastatic lymph nodes

Rachel N. Grisham, MD
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Director, Gynecologic Medical Oncology, Memorial Sloan Kettering Westchester
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West Harrison, NY/New York, NY

Targeted Oncology™: What factors do you consider when choosing a first-line maintenance regimen for patients with ovarian cancer?

GRISHAM: [Data from] recent studies, and multiple new FDA approvals, have led to a change in how we treat our patients in the upfront setting and [this is reflected in] the National Comprehensive Care Network [NCCN] guidelines.¹

The main point of these guidelines is that we should do molecular testing in all of our patients at the time of diagnosis and then consider those results when we [choose] first-line maintenance treatment options because we now have multiple FDA-approved options.

For all our patients with a BRCA mutation [in their tumor], it is recommended to give a PARP inhibitor if they have advanced-stage disease and have responded to chemotherapy.²³ For those patients who received bevacizumab [Avastin] in the front-line setting [and are] positive for HRD, it’s generally recommended to give the combination of bevacizumab with [the PARP inhibitor] olaparib [Lynparza]²; if they are HRD negative, we consider just continuing the bevacizumab by itself.¹ A lot of thought and discussion with the patient has to go into making these individual [treatment] decisions, which are based on a patient’s tolerance of their initial chemotherapy, their expected tolerance of the PARP inhibitors, and their individual molecular profile.

What data support the use of olaparib as maintenance therapy after first-line chemotherapy?

SOLO-1 [NCT01844986] is the phase 3 study [whose findings] led to the initial FDA approval of olaparib as a maintenance therapy for patients with a germline or somatic BRCA mutation following response to initial surgery and chemotherapy.⁴⁵ This study enrolled patients who had a BRCA mutation; it could have been germline or somatic but virtually all the patients enrolled in the study had germline mutations because that’s how we were testing back then.

The patients had newly diagnosed ovarian cancer and had received prior platinum-based chemotherapy. They were randomly assigned in a 2:1 ratio to receive either olaparib or a placebo, respectively, with investigator-assessed progression-free survival [PFS] being...
the primary end point. We now have more than 5 years of follow-up from this study, and the fantastic results were presented at the ESMO [European Society for Medical Oncology] Congress in 2020, which showed continued PFS benefit.

Recurrence occurred in only half the patients treated with olaparib vs in almost 80% of patients treated with placebo, at a median PFS of 56.0 months vs 13.8 months, respectively [HR, 0.33; 95% CI, 0.25-0.43]. Olaparib maintenance also produced a good duration of response. It is FDA approved for these patients and we strongly recommend that all our patients with a germline or somatic \textit{BRCA} mutation have front-line maintenance with a PARP inhibitor.

Additionally, all the subgroups benefited from the use of olaparib. These subgroups were defined by either a complete or partial response to chemotherapy, ECOG performance status, age, \textit{BRCA} mutation status—either \textit{BRCA1} or \textit{BRCA2}—and other criteria as well. These results suggest that all patients with a \textit{BRCA} mutation in their tumor are going to benefit from the use of a PARP inhibitor in the frontline maintenance setting. After 5 years of follow-up, the safety profile remained consistent and no additional cases of myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML] were reported.

The incidence of new primary malignancies was balanced between arms. I know we see different levels of MDS and AML in different studies, and some studies show higher rates of MDS and AML in patients who received more lines of chemotherapy, but I did find these data reassuring. Among patients treated with olaparib, common adverse events [AEs] included nausea and [other] gastrointestinal [GI] AEs such as fatigue, headache, and abdominal pain. We’re often able to mitigate [nausea-related] AEs with the use of anti-nausea medications.

\textbf{Niraparib [Zejula] is another PARP inhibitor. What data support its use in patients with high-risk ovarian cancer?}

The PRIMA trial [NCT02655016] examined niraparib vs placebo in the high-risk population of patients who had newly diagnosed ovarian cancer and had received neoadjuvant chemotherapy, or had stage IV disease, or had residual disease after debulking for stage III disease. Patients who were stage III and who had a complete gross resection were not eligible. This study looked at all comers, unlike the SOLO-1 trial in which all patients had a \textit{BRCA} mutation. The study was a double-blind, randomized, placebo-controlled phase 3 study and looked at patients who had achieved a complete response or a partial response following their first-line platinum chemotherapy. Patients were randomly assigned in a 2:1 ratio to receive either niraparib or placebo, respectively.

There was an amendment during this study to allow for a modified dosing schedule. Initially, all patients received 300 mg daily. Later, the study was amended to allow for a 200-mg starting dose for patients with lower platelet counts or lower body weight at the start of treatment. Similar results were found between those patients treated with the higher starting dose and the patients treated with the individualized starting dose.

The primary end point for the PRIMA study was PFS in all comers, regardless of \textit{BRCA} mutation status and regardless of HRD status. There was an improvement in PFS at 13.8 months with the use of niraparib maintenance therapy vs 8.2 months with placebo, with an HR of 0.62.
The toxicity profile is like that of olaparib, generally manageable with the use of conservative measures, supportive care, and dose reductions as needed, in addition to the individualized starting dose. Treatment discontinuation due to thrombocytopenia was relatively low, occurring in only 4.3% of patients, and dose interruptions were [similar to] those in previous niraparib trials.11

[As we would expect], there were more hematologic AEs [among patients who received niraparib]. I generally think of olaparib as causing more GI AEs and niraparib as causing more hematologic AEs, particularly thrombocytopenia, which can be severe, and anemia, [both of which were observed in the experimental arm of this study].

What trends in toxicity were observed among these studies?

You can’t directly compare the results of the different trials, of course, because the studies involved different populations of people. [However,] anemia and thrombocytopenia were observed more [often] in the PRIMA trial of niraparib than in the other 2 studies. Nausea and fatigue were observed more [often] in the SOLO-1 trial of olaparib, and for each of these AEs, the percentage of affected patients was similar between the other 2 studies.2,3,13 We generally [associate] hematologic AEs with niraparib and GI AEs with olaparib.

CASE (continued)

- The patient was treated with IV carboplatin and paclitaxel with aprepitant antagonists
- (NK1), ondansetron (5HT3 antagonist), and dexamethasone prophylaxis was used for chemotherapy-induced nausea and vomiting.
- She experienced persistent daily nausea with vomiting on day 1 after chemotherapy.
- After completion of chemotherapy, CA125: 14.2 U/mL; clinically no evidence of disease.
- The patient reported continuing daily nausea.

Has either niraparib or olaparib been examined in combination with any other treatment as part of a maintenance regimen?

The PAOLA-1 study [NCT02477644] was a phase 3 study that examined the combination of bevacizumab plus olaparib vs bevacizumab plus placebo as maintenance therapies. Patients in this study had newly diagnosed advanced ovarian cancer. They had completed their first-line surgery and platinum-based chemotherapy plus bevacizumab, and then had either a complete or partial response to their initial treatment. Patients in this study were allowed to have neoadjuvant chemotherapy, like patients in the PRIMA study, and could not have had prior PARP inhibitor therapy. In this study, olaparib was administered at a dosage of 300 mg twice a day.12

Overall, the patients who received bevacizumab plus olaparib had an improved PFS vs patients who received bevacizumab plus placebo [HR, 0.59; 95% CI, 0.49-0.72; P < .001]. This benefit was more pronounced in those patients who had BRCA mutations and in those patients who were HRD positive. Patients who were HRD negative [showed no benefit from receiving the experimental combination].15 For both the PRIMA study and PAOLA-1 study, HRD status was determined using the Myriad myChoice [CDx] assay to look for HRD, with a cutoff score of 42.11,14

In the PAOLA-1 study, patients experienced the AEs that we would expect from olaparib—nausea, fatigue, and some decrease in cell counts. [There were also] some bevacizumab AEs, including hypertension, but overall the AEs were manageable.13

POLLING QUESTION

At a live virtual event, Grisham asked participants, “What do you anticipate being your most commonly used approach to first-line maintenance in your patients with newly diagnosed BRCA wild-type or HRD advanced ovarian cancer?”

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TOTAL VOTES: 11
What dose adjustments are recommended to maximize the tolerability of these drugs?

[Dose adjustment] is important, I think, in making niraparib more tolerable. In the PRIMA study, initially, niraparib was given to all patients at a standard dosage of 300 mg once a day.

However, as previously mentioned, the study was amended to incorporate a patient-specific dosage based on the patient’s body weight and platelet count to make the regimen more tolerable. The results obtained with each dosage were similar.⁴⁻⁶

When starting niraparib, I always look at a patient’s weight and platelet count. First, I give the patient time, usually 4 to 6 weeks, to recover their platelet count after chemotherapy.

Then, if their body weight is 77 kg or greater and if they have a platelet count of 150,000/μL or higher, I start them at the full dose of 300 mg once a day. If their weight is less than 77 kg, which isn’t that low for shorter people, or if their platelet count is less than 150,000/μL, then the individual starting dose is 200 mg once a day. Using an individualized starting dose can [improve] the tolerability of niraparib and prevent [later] dose reductions necessitated by decreased platelets.⁵,¹⁶

Dose adjustments are also available for both olaparib and niraparib based on AEs such as persistent fatigue, persistent nausea despite medical management, and persistently decreased platelet counts despite individualized dosage. It’s a little more complicated to change the dosage of olaparib than that of niraparib, because in the case of olaparib you have to get prescriptions for new pills.

Olaparib’s starting dosage is 300 mg twice a day, and patients take two 150 mg pills per dose. If you want to do a dose reduction, the first dose reduction is to 250 mg twice a day; each dose consists of a 100 mg tablet and a 150 mg tablet, so you have to submit a new prescription for the 100 mg tablets. The second dose reduction is to 200 mg twice a day, using the 100 mg tablets. It is [a nuisance] to submit that new prescription but it is best to use this stepwise dose reduction for olaparib.²

Reducing the dose of niraparib is a little more straightforward. If the patient weighs 77 kg or more and has a platelet count of 150,000/μL or higher, you start them at the full dosage of 300 mg once a day. I usually tell my patients to take it in the evening, then they can have a dose reduction to 200 mg or 100 mg. If they start at a 200-mg dose, they can have a dose reduction to 100 mg, but after that, if [the drug is] not tolerated, I discontinue it.³

REFERENCES


5. FDA approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based. FDA. December 19, 2018. Updated December 26, 2018. Accessed January 20, 2022. https://bit.ly/3gmIcA


Case-Based Roundtable Meetings Spotlight

SKIN CANCER

Roundtable Discussion: Atlas Considers Sequencing for a Patient With Basal Cell Carcinoma

CASE SUMMARY

A man aged 88 years presented with a nonhealing ulcer on the lateral aspect of his nose. Biopsy demonstrated infiltrative basal cell carcinoma (BCC).

DISCUSSION QUESTIONS

- How do you stratify BCC to determine treatment options?
- Given this patient’s high risk for recurrence, what are the treatment options?

ATLAS: Based on the NCCN [National Comprehensive Cancer Network] guidelines on BCC, it’s important to think about it from a risk group stratification standpoint, which is low-risk vs high-risk lesions.¹

Low-risk lesions are typically present on the trunk and extremities; less than 2 cm in size; well-defined, primary lesions; not in immunosuppressed patients; no previous radiation to the site; nodular or superficial; and without perineural invasion.

High-risk lesions on the trunk and extremities are usually greater than 2 cm in size, so these are locally advanced lesions and in difficult places to treat such as cheeks, forehead, scalp, neck, and pretibial area. Anything that’s greater than 1 cm in these sites, I would call a high-risk lesion. The mask areas such as across the central face, the eyelids, eyebrows, periorbital, nose, and lips are high-risk areas, as well as the postauricular area, temple, and ear. They are poorly defined, recurrent lesions in patients who are immunosuppressed and occur in a site of previous radiation. They have perineural invasion and an aggressive growth pattern.

Based on the NCCN guidelines for locally advanced BCC (laBCC), which is what this patient has, and metastatic BCC (mBCC), systemic therapy may be considered. It is used where topical therapy, surgery, or radiation are not likely to be curative. Locally advanced disease is defined as primary or recurrent local disease not amenable to surgery or radiation. Multidisciplinary consultation is key in the treatment of these patients.¹

Systemic therapy options include hedgehog pathway inhibitors [HPIs]. [Because of] the frequency…of intolerable adverse events [AEs] associated with these inhibitors, drug holidays or even alternative dosing regimens need to be used to allow for improved adherence to therapy. This approach has been used for patients who have certain hereditary syndromes such as Gorlin syndrome. Current FDA-approved HPIs include vismodegib [Erivedge] and sonidegib [Odomzo].

There’s also an emerging role, and now an FDA approval, for immunotherapy in this setting with cemiplimab...
Indication
VITRAKVI (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. Select patients for therapy based on an FDA-approved test. 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 confirmatory trials.

Important Safety Information
Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.
In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.
Cognitive impairment occurred in 11% of patients. The median time to onset of cognitive impairment was 5.6 months (range: 2 days to 41 months). Cognitive impairment occurring in ≥1% of patients included memory impairment (3.6%), confusional state (2.9%), disturbance in attention (2.9%), delirium (2.2%), cognitive disorders (1.4%), and Grade 3 cognitive adverse reactions occurred in 2.5% of patients. Among the 30 patients with cognitive impairment, 7% required a dose modification and 20% required dose interruption.

Please see additional Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information.
Based on medical claims and prescription data claims for the period August 2019 through December 2020. Validated by IQVIA in March 2021.

NTRK and among 92 pediatric patients, fractures were reported in 7% of patients. Most fractures were associated with minimal or moderate trauma. Some fractures were associated with radiologic abnormalities suggestive of local tumor involvement. VITRAKVI treatment was interrupted due to fracture in 1.4% patients.

Promptly evaluate patients with signs or symptoms of potential fracture (e.g., pain, changes in mobility, deformity). There are no data on the effects of VITRAKVI on healing of known fractures or risk of future fractures.

Hepatotoxicity: In patients who received VITRAKVI, increased AST of any grade occurred in 52% of patients and increased ALT of any grade occurred in 45%. Grade 3-4 increased AST or ALT occurred in 3.1% and 2.5% of patients, respectively. The median time to onset of increased AST was 2.1 months (range: 1 day to 4.2 years). The median time to onset of increased ALT was 2.3 months (range: 1 day to 4.2 years). Increased AST and ALT leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 3 (1.1%) of patients.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

Embryo-Fetal Toxicity: VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily.
IN NTRK GENE FUSION–POSITIVE SOLID TUMORS, INHIBIT WHAT’S DRIVING THE TUMOR WITH VITRAKVI FOR:

**Robust responses**

In the primary data set (N=55)...

- **25% CR**<sup>a,b</sup> (n=14/55)
- **49% PR**<sup>a</sup> (n=27/55)

**75% ORR**<sup>a</sup> (95% CI: 61%, 85%) (n=41/55)

1 in 4 patients had a complete response<sup>1b</sup>

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**Demonstrated durability**

32.9-month mDOR<sup>c</sup>

(95% CI: 14.8, NE*)

(Range: 1.6+ to 50.6+ months)

**Observed DOR rates**

- 63% of patients with a response had an observed DOR >1 year
- 49% of observed responses lasted longer than 2 years

* mDOR, median duration of response; NE, not evaluable.
<sup>†</sup>Kaplan-Meier estimate.
<sup>+</sup>Denotes ongoing response.

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**Find the oncogenic driver early and act with VITRAKVI for appropriate patients**

TEST. TRK. TREAT.

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**Study design**: A pooled efficacy analysis based on 3 open-label, single-arm clinical studies in adult and pediatric patients with unresectable or metastatic solid tumors with an NTRK gene fusion. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Major efficacy outcome measures were ORR and DOR, as determined by a BIRC<sup>2</sup> according to RECIST<sup>3</sup> v1.1.<sup>1</sup>

<sup>1</sup>BIRC, blinded independent review committee; DOR, duration of response; RECIST, Response Evaluation Criteria In Solid Tumors.

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**Indication**

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test. 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 confirmatory trials.

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**Important Safety Information (continued)**

**Embryo-Fetal Toxicity (continued)**: Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

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**Most Common Adverse Reactions (≥20%)**: The most common adverse reactions (≥20%), including laboratory abnormalities, were: increased AST (52%), increased ALT (45%), anemia (42%), musculoskeletal pain (42%), fatigue (36%), hypalbuminemia (36%), neutropenia (36%), increased alkaline phosphatase (34%), cough (32%), leukopenia (28%), constipation (27%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (25%), vomiting (25%), pyrexia (24%), lymphopenia (22%) and abdominal pain (21%).

**Drug Interactions**: Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John’s wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

**Lactation**: Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

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

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Visit VITRAKVI.com

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VITRAKVI® (larotrectinib) capsules, for oral use
VITRAKVI® (larotrectinib) oral solution

Initial U.S. Approval: 2018

BRIEF SUMMARY OF PRESCRIBING INFORMATION PAGE 2 OF 2

1 INDICATIONS AND USAGE

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:
• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,
• are metastatic or where surgical resection is likely to result in severe morbidity, and
• have no satisfactory treatment options or that have progressed following treatment.
Select patients for therapy based on an FDA-approved test.
This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Central Nervous System Effects
Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, peripheral neuropathy, and sleep disturbances.
In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disturbances were observed in 42% with Grades 3-4 in 3.9% of patients.

5.2 Skeletal Fractures
Across these 279 patients, the median age was 46 years (range: 0.1 days to 84 years); 33% were female. The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from 92 pediatric patients, fractures were reported in 9% (N=279; 8%). Median time to fracture occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, peripheral neuropathy, and sleep disturbances.

5.3 Hepatotoxicity
In patients who received VITRAKVI, increased AST of any grade occurred in 52% of patients and increased ALT of any grade occurred in 45% of patients. Grade 3-4 increased AST of ALT occurred in 2.1% and 2.5% of patients, respectively [see Adverse Reactions (6.7)]. The median time to onset of increased AST was 2 months (range: 1 day to 4.2 years). The median time to onset of increased ALT was 1.7 months (range: 1 day to 4.2 years). Increased AST and ALT leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 3 (1.1%) of patients.

5.4 Embryo-Fetal Toxicity
Based on literature reports in human subjects with congenital malformations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily and 6.1 Clinical Trial Experience
The following clinically significant adverse reactions are described elsewhere in the labeling: Central Nervous System Effects [see Warnings and Precautions (5.1)]; Skeletal Fractures [see Warnings and Precautions (5.2)]; Hepatotoxicity [see Warnings and Precautions (5.3)].

6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Unless noted, data in WARNINGS AND PRECAUTIONS and below reflects exposure to VITRAKVI in 279 patients, including 54% patients exposed for greater than 6 months and 30% patients exposed for greater than 1 year. One adult dose-finding trial (LOXO-TRK-1-001 [n = 21]) and one pediatric dose-finding trial (SCOUT [n = 88]) and one single arm trial (NAVIGATE [n = 116]).
All patients had an untreated NTRK-rearranged solid tumor and no satisfactory alternative treatment options or disease progression following treatment.

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

7.1 Effects of Other Drugs on VITRAKVI
Avoid coadministration of VITRAKVI with sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Drug Interactions (7.4)].

7.2 Drug Interactions
Larotrectinib clearance was reduced in subjects with moderate (Child-Pugh B) to severe (Child-Pugh C) liver impairment.

8 DRUG INTERACTIONS
VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective contraception during treatment and for 1 week after the final dose of VITRAKVI [see Use in Specific Populations (8.2)].

9.2 Pregnancy
Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

9.3 Nursing Mothers
Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

9.4 Pediatric Use
VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

9.6 Patient Counseling
Advise patients and caregivers to inform their healthcare provider of all concomitant medications, concomitant medical conditions, and laboratory abnormalities.

10 OVERDOSAGE

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

11.2 Pharmacodynamic Properties

11.3 Pharmacokinetics

11.4 Special Populations

11.5 Postmarketing Surveillance

11.6 Animal Data

11.7 Nonclinical Toxicology

11.8 Clinical Trials

11.9 Drug Interactions

11.10 Carcinogenesis, Mutagenesis, Impairment of Fertility

11.11 Laboratory Findings

11.12 Other Precautions

11.13 Selected Postmarketing Reports

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11.18 Nonclinical Pharmacology

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11.22 Drug Interactions

11.23 Carcinogenesis, Mutagenesis, Impairment of Fertility

11.24 Laboratory Findings

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11.26 Postmarketing Surveillance

11.27 Nonclinical Toxicology

11.28 Nonclinical Pharmacology

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamic Properties

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12.10 Carcinogenesis, Mutagenesis, Impairment of Fertility

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12.14 Additional Information

12.15 Information for Patients

12.16 Information for Healthcare Providers

12.17 Reference Information

12.18 Nonclinical Pharmacology

12.19 Nonclinical Toxicology

12.20 Clinical Pharmacology

12.21 Clinical Trials

12.22 Drug Interactions

12.23 Carcinogenesis, Mutagenesis, Impairment of Fertility

12.24 Laboratory Findings

12.25 Special Populations

12.26 Postmarketing Surveillance
The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in adult or pediatric patients 28 days and older [see Adverse Reactions (6.1), Clinical Studies (14)]. The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in the Clinical Studies section (see Clinical Studies (14)). The safety of VITRAKVI was evaluated in 92 pediatric patients who received VITRAKVI. Of these 92 patients, 36% were <1 month to <2 years (n = 33), 41% were 2 years to <12 years (n = 38), and 23% were 12 years to ≤18 years (n = 21). 29% had metastatic disease, 42% had locally advanced disease, and 27% had primary CNS, and 86% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were infantile fibrosarcoma (37%), primitive neuroectodermal tumor (24%), and neuroblastoma (7%). The median duration of exposure was 7.4 months (range: 0.4 months to 39 months).

Due to the small number of pediatric and adult patients, the single arm design of clinical studies of VITRAKVI, and the confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to VITRAKVI are related to patient age or other factors. Adverse reactions occurring more frequently (at least a 10% increase in per-patient incidence) in pediatric patients compared to adult patients were pyrexia (45% versus 13%), vomiting (42% versus 17% in adults), diarrhea (35% versus 23% in adults), rash (28% versus 15% in adults), upper respiratory tract infection (23% versus 8% in adults), nasopharyngitis (16% versus 6% in adults), and otitis media and rhinitis (each 14% versus 0.5% in adults).

Laboratory abnormalities occurring more frequently (at least a 10% increase in per-patient incidence) in pediatric patients compared to adult patients were AST increased (63% versus 49% in adults), neutropil count decrease (86% versus 16% in adults), leukocyte count decrease (39% versus 27% in adults), hyperkalemia (36% versus 13%), and lymphocyte increase (24% versus 9.2%). Two of the 92 pediatric patients discontinued VITRAKVI due to an adverse reaction (Grade 3 increased ALT and Grade 4 increased AST).

The pharmacokinetics of VITRAKVI in the pediatric population were similar to those seen in adults [see Clinical Pharmacology (12.3)].
[Libtayo] for patients with laBCC or mBCC previously treated with an HPI or in those for whom an HPI would not be appropriate. This also includes patients who had stable disease or lack of response after several months of therapy.¹²

**DISCUSSION QUESTION**
Would you give cemiplimab as frontline therapy for this patient and why?

**ABHISHEK:** Cemiplimab has a history in skin cancer; it is well tolerated and can offer a decent response as well as durable response. So why not?

**KHAN:** We have much more experience and comfort levels with prescribing immunotherapies, so...our thresholds to use these drugs are lower compared with a new drug like an HPI. Familiarity with immunotherapy makes us pull the trigger quick.

**HAGAN:** I would love to use it, and...the major concern would be my understanding of the FDA approval is that it is approved for use after an HPI or in those for whom an HPI was not thought to be appropriate. A lot...would depend on how strict the insurance companies were about using it. I think most oncologists are seriously in love with immunotherapy and molecularly targeted therapy. The fact that we have 2 drugs in this situation that we could use is awesome. But whatever I could get for the patient, I’d try to get.

**YUAN:** I have very little experience using both HPIs as well as cemiplimab. From my very limited experience, I will choose the immunotherapy because of HPI AEs, such as the [debilitating] fatigue for my patient. That’s all I’m thinking, maybe just to choose immunotherapy [because] it’s a little bit better tolerated.

**ATLAS:** What I’m hearing is that we in the oncology world, whether you predominantly treat skin cancers or general oncology, have a lot more familiarity with using immunotherapy and are well versed in its AEs. I [would not use cemiplimab]. The indication truly is for patients who have either a contraindication to an HPI, have failed an HPI, or had intolerance to therapy. These indications were listed on the trial [NCT03132636] that led to the approval of cemiplimab.³ In my practice, if he did not have a contraindication, I would at least attempt therapy with an HPI first.

**CASE UPDATE**
The patient was started on vismodegib 150 mg by mouth daily. By 2 months on therapy, he experienced painful joints and muscle spasms; he lost 10 lb since treatment initiation. His muscle pain did not significantly improve with nutritional/hydration counseling, physical therapy, or amlodipine. Additionally, he experienced dysgeusia.

**DISCUSSION QUESTION**
What would you do next, and what would trigger you switching from an HPI?

**ABHISHEK:** If the patient had a good response, at least from the local standpoint, I think a drug holiday would be appropriate. Is the patient at a point that they could have more surgery? That would be a consideration at this point, as well.

**ATLAS:** A drug holiday was an option, and that’s a great choice. [Another option is an] amenable surgical plan. Often in my team, this includes multiple [surgeries]. He’s had nice closure over the nose. I usually do repeat biopsies around the original periphery to see whether we have active disease.

We could think about treatment discontinuation if we had negative biopsies and could move on to observation. I think one other thing to consider if we still have active disease—because it’s not an aesthetic location or a location amenable to local regional management—is moving to an intermittent dosing pattern. One trial that specifically looked at this...is the MIKIE trial [NCT01815840], which was a phase 2 trial that looked at 2 different intermittent dosing regimens. One was using vismodegib for 3 months on, followed by an 8-week drug holiday.

That is something I incorporate into my strategy for treating these patients often. They also had an alternative regimen doing a 6-month lead-in of vismodegib followed by a 2-month-on, 2-month-off treatment pattern to allow for drug intolerance.⁴ Then there is the immunotherapy option that we could move to for a patient who had intolerance to HPIs. Those would be some of the options I would see at this point for this patient.

**KHAN:** Why is dose reduction not an option?

**ATLAS:** They did not look at dose reduction in any of these clinical trials of the 150-mg tablet, which is

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the tablet size for vismodegib. So there’s not really a drug reduction option, and we typically don’t ask that patients divide these tablets from an administration standpoint. I’ve seen dermatologists sometimes go to every-other-day dosing. I find...that the time frame for people to recover from the toxicities takes longer than that.

I don’t usually find that it makes a huge difference going to every-other-day or every-third-day dosing patterns, and that’s why I typically take these longer breaks off if tolerated.

Khan: Why does the company not try them? They had studies with the 2-month-on, 2-month-off regimen, so why not come with a lower dose [because] that may pan out and make it more tolerable?

They could have some of it in smaller-dose tablets as well, if they know that it [decreases] problems.

Atlas: They would have to do pharmacokinetic studies and prove benefit, which haven’t been done. But it’s a good question.

Yuan: In case you give a drug holiday and the cancer has recurred...do you rechallenge with an HPI or just switch to the immunotherapy?

Atlas: Previously, when we did not have the FDA-approved immunotherapy option, you could rechallenge. People can still have excellent responses with rechallenge. The bigger aspect is, can they have tolerance to the drug?

That’s what I’ve noted in my clinical practice. If I rechallenge and someone is intolerant to the drug, then I immediately would shift to immunotherapy. Also based on the grade and number of toxicities, I will often think about shifting to immunotherapy in that setting.

**CASE UPDATE**

Vismodegib was held for 2 weeks. Symptoms returned after reinitiation. The patient preferred not to continue therapy.

**DISCUSSION QUESTIONS**

- How should eligibility for a HPI be determined?
- What do we know about patients who received PD-1 inhibitor prior to HPI therapy?
- Do you have experience with this?
- Are there specific patients for whom you would use cemiplimab as first-line therapy?

Atlas: In my...practice, moving from one of the HPIs to the other has not, traditionally, overcome resistance if someone’s progressing, or having intolerance, because they share many of the same AEs. But it is a strategy that could be considered.

HPI eligibility should be determined by a medical oncologist. There are dermatologists who prescribe, in many areas, and so a clinical evaluation [is needed to assess] whether somebody has a surgical option, a radiation option, or whether systemic therapy is the ideal option....Do they have a low-risk or a high-risk lesion? Do they have some sort of comorbidity that excludes them or [that] we think is going to have a high rate of toxicity? These would be the patients I might think about not starting with an HPI and moving toward immunotherapy.

For patients who’ve received anti–PD-1 therapy prior to a HPI, we don’t have any clear data on that. In my...clinical practice, which revolves around treating cutaneous malignancies, I have many patients who’ve had multifocal tumors, whether it is BCC, cutaneous squamous cell carcinoma, or they have more than 1 diagnosis like melanoma plus another disease.

I do have some experience in giving PD-1 therapy before someone gets an HPI and it can be very successful as a frontline approach...It’s reasonable to use for the right patient in the frontline setting, although the current FDA approval would be for use after an HPI unless the patient’s not a candidate.

Khan: I think it is also [an option] for somebody who is not [adherent] on oral drugs.

Atlas: That’s a really good answer, and that’s a problem we have in oncology. I think part of the problem with laBCC sometimes is, it was a neglected lesion. If we can’t rely on the patient to consistently take the drug, should we be starting with an intravenous medication?

Hanna: I have not [given frontline PD-1 therapy], but my understanding is [most] patients with BCC have a high tumor mutational burden [TMB] and typically patients with a high TMB have a higher chance of responding to immunotherapy. To me it makes sense to use it up front. It’s a good idea, but we need to have a clinical trial behind that.

Khan: I think the other rationale is that the duration of response from the immunotherapy, even as a second-line agent, seems to be decent. You would hope that you can use an up-front immunotherapy that can provide durable control, like you’ve seen in other malignancies that use immunotherapy, rather than a short-lived [response].
KHAN: A very important goal in locally advanced disease is providing good long-term disease control by surgical resection after a good response.

The rational designer drug approach would be where you say, “This patient is going to benefit from PD-L1 [agents] and this one is going to benefit from an HPI.” Have a target, so that I can be more educated in this age where I’m trying to use rational approaches rather than throwing drugs at [individuals].

HAGAN: You’ve already touched on trying to know the ideal sequencing. We got burned in lung cancer, when our EGFR-mutated cancers turned out to be strongly PD-L1 positive, but when we used the PD-L1 agent first, there was no response rate and then toxicity was worse when we went to osimertinib [Tagrisso], a drug that would have worked better if we had just waited for the EGFR [test] to come back.

I also think having 1 target is probably suboptimal. It would be nice if we could find some other targets; like with colon cancer, for example, we can target angiogenesis and we can target EGFR. Hopefully someday, we’ll be able to target KRAS. Finding other targets, so we could have nontoxic therapies, would be great. It seems like already a lot of these patients are somewhat older, their skin is in terrible shape, and they have more than 1 cancer.

REFERENCES
CHRONIC LYMPHOCYTIC LEUKEMIA

Awan Compares BTK Inhibition and Other Treatments for a Patient With CLL

CASE

• A 61-year-old woman reported symptoms of unintentional weight loss and increasing fatigue.
• Medical history: hypertension, medically controlled; history of asymptomatic atrial fibrillation (AFib)
• Physical examination: axillary lymphadenopathy, spleen palpable approximately 6 cm below costal margin; appears chronically ill and continues only limited daily activity
• Laboratory results:
  ◦ White blood cell count: 47,000 /μg; 76% lymphocytes
  ◦ Hemoglobin level: 8.7 g/dL
  ◦ Platelets: 115,000 mm³/μL
  ◦ Absolute neutrophil count: 3600 mm³/μL
  ◦ Lactate dehydrogenase level: 250 U/L
  ◦ β₂-Microglobulin level: 4.3 mg/L
  ◦ Flow cytometry: CD5+, CD20+, CD23+
  ◦ Fluorescence in situ hybridization: 11q deletion (del[11q])
  ◦ Molecular analysis: IGHV unmutated
  ◦ Bone marrow biopsy: diffuse infiltration by chronic lymphocytic leukemia (CLL)

Farrukh Awan, MD
Associate Professor, Department of Internal Medicine
University of Texas Southwestern (UTSW) Medical Center
Member, UTSW Harold C. Simmons Comprehensive Cancer Center and William P. Clements Jr. University Hospital
Dallas, TX

Targeted Oncology™: What are the National Comprehensive Cancer Network (NCCN) guidelines for treating a patient with CLL?

AWAN: The final product that [came] out from the NCCN is very complicated, and there are a lot of things on the recommendations that we don’t necessarily agree with. A lot of that has to do with how the guidelines have evolved. There is also a lot of opinion and only a few things have a clear category 1 recommendation. A lot of the recommendations are in the gray area. The idea is that the NCCN guidelines have to be universally adaptable and usable. Therefore, as long as there are some data to support the utility of a certain regimen, it will stay on the guidelines; we don’t want to eliminate those options because these guidelines are used by insurance providers to justify coverage. There are other reasons for the many options listed in the guidelines, even though we would never use some of them in our regular practice.

Having said that, we should focus on the main regimens because that’s where there is very little discussion in the community. These are acalabrutinib [Calquence] plus obinutuzumab [Gazyva], ibrutinib [Imbruvica], and venetoclax [Venclexta] plus obinutuzumab.¹ These regimens can be used for [almost all] patients including those with low risk [or] high risk, young and old. There are also variations based on comorbid conditions, patient age, and other factors.

There are other guidelines, which some of you might use, that indicate a preference for 1 option. From my experience that would not be ibrutinib anymore. That’s interesting because the field is already evolving and ibrutinib has been the established front runner for a long time. But there’s a lot of debate. I’ll share some very interesting recent data and my personal concerns, as well as the positives and the negatives, in a transparent way.

The bottom line is that our 3 options [for treating CLL] are acalabrutinib with or without obinutuzumab, ibrutinib, and venetoclax/obinutuzumab. Having said that, around 20% to 30% of patients in this country are treated with bendamustine/rituximab [Rituxan], which is still a very commonly used regimen. Other options are single-agent rituximab for really old patients. I think those are still being used in a sizable number of patients despite the fact that we have some very good and effective nontoxic or relatively less toxic options.

I think there is consensus among most of us that those are the regimens we should stick to. If you look at the footnotes in the NCCN criteria, they summarize the discussion points.

¹ Reference: Awan identifies these regimens as the primary options due to their established use across different risk categories, despite variations in other guidelines.
What I found surprising was that, at 4 years out, the median PFS [in Elevate CLL TN] was 87% [with obinutuzumab/acalabrutinib] vs 78% with acalabrutinib alone. So the additional obinutuzumab is improving PFS by 9%. That’s not trivial. It’s definitely encouraging to see that if these patients are followed for long enough, they might have a better outcome.”

—FARRUKH AWAN, MD

...It’s nice to focus on and read those footnotes to understand how the decisions on what to include were made because we all try to justify our opinions and that’s sometimes interesting to read. For example, recently there was a debate about what to say regarding the BTK [Bruton tyrosine kinase] inhibitors acalabrutinib and ibrutinib and proton pump inhibitors, and whether we should recommend one over the other. There were a lot of arguments back and forth and finally it was all summarized in the footnote. The footnote elaborates on what we suggest and what to consider when selecting a specific agent as that could make a huge difference.

What are the data behind using acalabrutinib plus obinutuzumab for patients with CLL?
The Elevate CLL TN study [NCT02475681] compared acalabrutinib vs acalabrutinib plus obinutuzumab.2 The thought was the addition of a newer CD20 antibody might be better than rituximab. The study also had a standard [obinutuzumab/chlorambucil] control arm for patients younger than 65 years who had a lot of comorbid conditions or patients older than 65 years—basically patients who would historically not be considered candidates for chemotherapy.

The updated 4-year results are very interesting. It is obvious that the acalabrutinib-containing arms are significantly better than the comparative chlorambucil/obinutuzumab arm. I don’t think anybody was surprised by that. What I found surprising was that, at 4 years out, the median PFS [progression-free survival] was 87% vs 78% with acalabrutinib alone.2

So the additional obinutuzumab is improving PFS by 9%. That’s not trivial. It’s definitely encouraging to see that if these patients are followed for long enough, they might have a better outcome. Therefore there is some evidence that the additional CD20 antibody might improve our lives, as this is the best result that we have seen so far. The trial was not designed to study this difference so we cannot comment on it too much because that was not one of the primary end points. But that is a very provocative finding and when we saw the 3-year outcomes, it was beginning to separate, and now at 4 years, it’s definitely more separated and the obinutuzumab-containing arm is doing well. So that’s why this is an important study.

Patients who have IGHV mutations do well regardless of treatment and they have a fairly good outcome with chlorambucil and obinutuzumab. Even in those patients, the acalabrutinib arms looked better. Obviously, for IGHV unmutated, more aggressive [disease], the acalabrutinib arms were significantly better and there was a dramatic difference.2 One thing we have seen consistently is that the IGHV mutation status does not matter for treatment with a CD20 antibody or for that matter with acalabrutinib alone. Both of those regimens are doing well.

As expected, most responses are PRs [partial responses].2 There is a slightly higher complete remission rate with the addition of obinutuzumab, as expected. The additional obinutuzumab also increases the undetectable MRD [minimal residual disease] rates, and the deeper the remission, the longer it lasts. But there’s also a lot of debate about what level of MRD you need. I think the MRD story needs a little more work. But that’s definitely one of the surrogates we have and, in this study, the MRD undetectability level was 10−4. That’s what we would call a medium MRD. It’s very difficult to demonstrate a survival advantage with a lot of the newer CLL agents as there will be a lot of crossover and people will go from one arm to the other. So survival is pretty good for our patients [and] that’s encouraging.
What was the toxicity profile in Elevate CLL TN?
A lot of the debate is focused on the safety. The most common problem that we see with any CLL trial is pneumonia. Infusion reactions are very minimal and are not a big problem as they can be managed fairly easily with premedication. In fact, starting acalabrutinib or a BTK inhibitor a few days before obinutuzumab results in 0 reactions. If you start the obinutuzumab on the same day as the acalabrutinib or ibrutinib, you will have a few more problems, but even 3 days makes a huge difference. Febrile neutropenia and tumor lysis are not a problem.

It was encouraging that the AFib, bleeding, and hypertension rates were fairly low; however, they were not 0. The big question raised was whether the 7% incidence of AFib was a real effect from the drug or just background. But in the control arm the AFib rates were very low, indicating that there was some drug effect. But it was encouraging that it was only around 7%. The hypertension rate was higher than that in the control group but not dramatically. Bleeding was definitely a problem, including major bleeding, although at a very low incidence.

We are used to seeing 5% to 10% major bleeds and up to 30% minor bleeds. Here the minor bleeds were around 30% but the rate of major bleeds was fortunately very low. That’s excellent. The big problem that all serial patients deal with is infection. Neutropenias are common especially in the first cycle and with the addition of obinutuzumab. Another problem with acalabrutinib is headaches, which respond very nicely to caffeine. So this is what we saw with the Elevate CLL TN study. It clearly showed improvement in outcomes with acalabrutinib and a possible trend toward better outcomes by the addition of obinutuzumab.

How has ibrutinib plus rituximab been studied for patients with CLL?
The ECOG-E1912 trial [NCT02048813] was a very important large cooperative US study comparing ibrutinib plus rituximab to FCR [fludarabine, cyclophosphamide, and rituximab] with 2:1 randomization. The study was designed for young patients who were eligible for chemotherapy.

There was a clear statistically significant improvement in survival within 3 years. These results should settle the debate of whether FCR or ibrutinib is better, even for the purists who want to see a survival advantage, which is very difficult to demonstrate in patients with CLL. Ibrutinib was clearly better.

The debate remains regarding which regimen is better depending on the IGHV-mutation status. In patients [with] IGHV mutations, the cases are so low at 3 years that there was no significant statistical difference. But it was getting close to being significant—88% at 3 years with IGHV-mutated [disease] and ibrutinib vs 82% [with FCR]. So the curves are beginning to separate in favor of ibrutinib. On the unmutated side, there is no question that ibrutinib is better and we feel that after 4 or 5 years of follow-up, the mutated patients will also be better in terms of PFS. The bottom line is that survival is also getting better for all patients and this is why everyone has moved on from FCR.

What is the evidence for the use of venetoclax for patients with CLL?
The CLL14 trial [NCT02242942] is a German study with patients who have comorbid conditions that were not ordinarily considered candidates for chemoimmunotherapy. Patients were assessed using the Cumulative Illness Rating [Scale], which assesses the comorbid burden but is a cumbersome tool to use. It assigns a point to almost everything, such as having eyeglasses, and therefore it is easy to get a score of 5 or 6. CLL14 was a fairly simple trial comparing venetoclax with obinutuzumab vs obinutuzumab plus chlorambucil.

Venetoclax was better than obinutuzumab [in terms of PFS]. As for the IGHV-mutation status, patients with unmutated IGHV were a little bit worse [off] with the venetoclax compared with patients with mutated IGHV. Now, we know that that’s a characteristic of the disease, but comparing the 2 treatment arms there’s a clear difference between venetoclax and obinutuzumab for both mutated and unmutated patients; the venetoclax arm is better than the chlorambucil/obinutuzumab arm.

Probably the most important results from this study were the differences between patients with or without del(17p) or TP53 mutations. Patients without these markers do very well, but those with these markers do poorly and don’t seem to plateau despite being on venetoclax and regardless of MRD status. Venetoclax has an obvious advantage that is well known: It gets patients into a deep remission.

But if you stop therapy after 12 months, these patients have a pretty poor outcome, almost as bad as patients who didn’t get venetoclax. So this is one group of patients that we have to be very careful about. There are different ways to manage these patients. Most of us in the CLL community are not stopping therapy for these patients because patients relapse very quickly after they stop the venetoclax at 12 months.

Did MRD play a role in the CLL14 data?
The MRD data clearly show that venetoclax produces a deep remission in the bone marrow and the peripheral blood. Having said that, what we don’t talk about is that there is a group of patients on venetoclax in a MRD-negative state (10⁶) despite the fact that they continue on venetoclax. So they have disease progression...
INDICATION AND USAGE
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

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

WARNINGS AND PRECAUTIONS

Cutaneous Reactions
Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

Monitor patients for new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression
Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%.

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions
Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.
Cutaneous Reactions (continued)
Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity
Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

ADVERSE REACTIONS
In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.
In LOTIS-2, serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.
Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.
Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.
Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to ADC Therapeutics at 1-855-690-0340.

Please see Brief Summary of the full Prescribing Information on adjacent pages.
ZYNLONTA™ (loncastuximab tesirine-lpyl) for injection, for intravenous use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

INDICATIONS AND USAGE
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Effusion and Edema. Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 4 or pericardial effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, or/and ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression. Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as appropriate.

Infections. Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or higher infections, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions. Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity. Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose (see Use in Specific Populations [8.1, 8.3]).

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

Effusion and Edema
Myelosuppression
Infections
Cutaneous Reactions
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADC-402-201 (LOTIS-2) and ADC-402-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles. In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies [see Clinical Studies (14.1)]. The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reduction due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2

<table>
<thead>
<tr>
<th>ZYNLONTA (N=145)</th>
<th>All Grades (%)</th>
<th>Grades 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>1+</td>
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<tr>
<td>Edema</td>
<td>28</td>
<td>3</td>
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<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Rash</td>
<td>30</td>
<td>2</td>
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<tr>
<td>Pruritus</td>
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<td>0</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
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<td>2</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
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<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>0</td>
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<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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In LOTIS-2, 0% of 134 patients tested positive for antibodies against loncastuximab tesirine-lpyl. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-lpyl. The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

Lactation

Risk Summary

There is no data on the presence of loncastuximab tesirine-lpyl or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

Females and Males of Reproductive Potential

ZYNLONTA can cause fetal harm when administered to pregnant women.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating ZYNLONTA.

Contraception

Females Advise women of reproductive potential to use effective contraception during treatment and for 9 months after the last dose.

Males Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 6 months after the last dose.

Infertility

Males Based on the results from animal studies, ZYNLONTA may impair fertility in males. The effects were not reversible in male cynomolgus monkeys during the 12-week drug-free period.

Pediatric Use

Safety and effectiveness of ZYNLONTA in pediatric patients have not been established.

Geriatric Use

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin is upper limit of normal [ULN]) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).
at the molecular level despite being on venetoclax. That doesn’t happen in a lot of patients; it happens in only a small percentage. But the fact is that MRD negativity even at the $10^{-6}$ level is not this magical cut-off that guarantees a full remission.

Now, why does that happen? We don’t know. Why [do] the patients with MRD-negative disease, despite having TP53, relapse? And why do they have inferior outcomes? There aren’t answers for that and this is an area of active research. So while it is good to get into deep remission and stop therapy after 12 months, ultimately what is important is the longevity of the patient.

Can you control the disease over 10 or 15 years and can you achieve that with venetoclax? Maybe you’ll have to do venetoclax after 4 or 5 years. The goal is that a 61-year-old patient could live an average of 20 more years at least, with 80 years being the average life expectancy. If you want your patient to live 20 years, how will you get to that 20-year mark? There is no right or wrong answer, so you can either do venetoclax and then venetoclax again and then venetoclax again, maybe 2 or 3 times to get to 20 years. Or maybe you can continue with the pill once or twice a day and they might get to the same end point. That is the debate.

The 4-year PFS rate with venetoclax and obinutuzumab was 74%, with acalabrutinib it was 79%, [and] with acalabrutinib and obinutuzumab it was 89%. Now it gets interesting. I know we shouldn’t compare one trial [with] another but remember, these trials had very similar populations and this is a 15% difference. That is provocative and that’s the big question and I don’t know the answer to that.

Tumor lysis syndrome [was] a big issue—it’s what made venetoclax famous early on—but frankly, it’s been a while since we saw tumor lysis with venetoclax. It just doesn’t happen that much if you prime the patients well. The way I do it is that I do the CD20 antibody first. I debulk the patients and after 2 months, I can easily do the escalation as an outpatient [procedure] without having to admit the patient for tumor lysis monitoring.

My biggest challenge with using venetoclax in the frontline or in the relapse setting is not tumor lysis; it’s cytopenias. When you do day 1, 2, 8, and 15 of obinutuzumab, if you do venetoclax concurrently, you will invariably have to stop one or the other because of cytopenias, primarily neutropenia or thrombocytopenia. That’s also what we saw in the study, that the neutropenia and thrombocytopenia were the most common issues. So what I typically do as I get the patient through the first cycle…is make sure that their white [blood cell] count has declined and that their lymph nodes are resolved, and then we can start venetoclax as an outpatient.
MUltiple Myeloma

Roundtable Discussion: Targeted Therapies for Relapsed/Refractory Multiple Myeloma

**CASE**

In 2017, a Black man aged 55 years in a rural community received a diagnosis of multiple myeloma, hyperdiploid, Revised International Staging System stage II. His medical history includes hypertension controlled with lisinopril. He received VRd (bortezomib [Velcade], lenalidomide [Revlimid], dexamethasone) for 4 cycles, followed by autologous stem cell transplant. The patient achieved a very good partial response (VGPR) and received lenalidomide maintenance, planned until progression.

At follow-up 3 years later (2020), the patient had stable disease on imaging. Laboratory results: hemoglobin, 11.3 g/dL; calcium, 9.2 mg/dL; creatinine, 0.8 mg/dL; and rising M protein. Cytogenetics showed deletion 17p (del[17p]) and hyperdiploid. His ECOG performance status was 0. The patient received D-Vd (daratumumab [Darzalex], bortezomib, dexamethasone).

One year later (2021), MRI showed new lytic lesions. The patient’s ECOG performance status was now 2. Laboratory results: hemoglobin, 11.5 g/dL; calcium, 9.8 mg/dL; creatinine, 1.1 mg/dL; M spike of 1.1 g/dL; and β₂-microglobulin was 5.6 mg/L. Repeat bone marrow biopsy showed del(17p) in 50% of cells, hyperdiploid.

**POLLING QUESTION**

“What are you most likely to recommend for this patient now?”

- CAR T-cell therapy 33% (4)
- Other 25% (3)
- Belantamab mafodotin 17% (2)
- Second ASCT 17% (2)
- Clinical trial 8% (1)
- Selinexor/dexamethasone 0% (0)

TOTAL VOTES: 12

**SHAIN:** My only comment here is when we look at what he has been through. We probably need a line of therapy before we get belantamab mafodotin [Blenrep] and CAR [chimeric antigen receptor] T-cell therapy approved, because [it’s] only the third line of therapy we were on. I would say there’s still carfilzomib [Kyprolis], pomalidomide [Pomalyst], and dexamethasone left over as another line of therapy. But...an important factor here is the enthusiasm around CAR T because this is something that I would share as well.

**SHAIN:** What goes into thinking of next line? We think about risk...


**DISCUSSION QUESTIONS**

- What are the key factors that influence your decision-making for a patient like this?
  - What if this patient had mild to moderate renal impairment?
  - What if this patient had cataracts? History of cataract surgery? Another ocular comorbidity?
  - What if this patient had an infection?
- What are the challenges of treating patients such as this one?

**CASTANEDA PUGLIANINI**: Yes, I completely second what you’re saying about referring the patient early, as soon as you’re thinking about CAR or thinking CAR is in the future for this patient. Yes, the sooner the better, so we can deal with the logistics around the CAR T treatment.

Things that you’re mentioning, like renal insufficiency, are important to consider in what is going to be the next line of therapy. I think this patient still has some options that are a standard of care. But the other thing that we want to transmit to our partners is that a clinical trial is also very important. This patient has already been exposed to a proteasome inhibitor and anti-CD38 antibody, has progressed on those, and has also seen transplant.

A clinical trial, which could include CAR T—there are cohorts in some of the studies ongoing—or bispecifics, that [is something] this patient may be eligible for. Those are the other things that we also need to keep in mind because that’s the only way we are going to keep learning about how we are going to be sequencing things before or after CAR T.

The other thing I think about is extramedullary disease—this patient, with what looks like clonal evolution now, 50% of the marrow involvement with del(17p). Those are things that heavily impact what the next step is for this patient.

**SHAIN**: Not just immunotherapy clinical trials, but...lots of other therapies...are being developed and need trials and...patients. Patients need them to manage their disease, so always think of that as your first thing.

**PARRONDO**: I would agree with Dr Castaneda [Puglianini’s] comment. I chose clinical trial. The patient only had 2 lines of treatment, so he doesn’t qualify for Abecma [idecabtagene vicleucel] or Blenrep yet. He’s triple-class refractory, so he would meet criteria for most clinical trials. I don’t like that he has del(17p); that makes me a little anxious, the clonal evolution, so I would try to get him on a B-cell maturation antigen [BCMA] bispecific T-cell engager [BiTE] or a CAR T trial, whichever slot I had open.

**MALHOTRA**: What would keep me away from using [certain therapies] would be if somebody already had eye issues; that’s quite important in terms of how the eye monitoring [must] be done.

**DISCUSSION QUESTIONS**

- Have you used belantamab mafodotin?
- What are your experiences or perceptions of this agent?
NAHAS: I’ve used it before. You’re talking about a 30% ORR, with 2% [stringent] complete response [CR] rate seen in the DREAMM-2 trial [NCT03525678]. The 1 patient I used it in had exactly that, almost no response. I’ve been a little underwhelmed by the regimen in a setting of a new target, which is something that was attractive to a triple-class refractory patient. It is a little bit burdensome with regard to coordination with eye [examinations] and whatnot, as well.

PARRONDO: I’ve used it. I usually start with a 2.5-mg dose. Almost everyone gets keratopathy. When that starts to happen, I lower the dose to 1.92 mg and I give it every 6 weeks. That seems to be better tolerated. In a patient, I combined it with low-dose thalidomide [Thalomid]; she’s been on that combination for a year and it was...remarkable. She had nonsecretory disease with a lot of skeletal lesions. They all went away. I drop the dose almost always and space out the interval.

GREENBERG: I have used it as well...it’s cumbersome because patients have to get eye exams before they start the therapy, then before each dose....Aside from that, my impression of the response data, the responses that I’ve seen in my patients, [is] it’s been limiting.

I think now, with BCMA-directed CAR T-cell therapies, that is probably going to be my way to go, prior to using belantamab mafodotin.

SHAIN: Yes, it can be, without question....My experience is not too dissimilar to what we’ve heard already. I’ve had some very nice responses and control of disease over time. I think Dr Parrondo hit it on the nose—we [must] think about what the dosing schedule looks like, making it easier for patients both from a toxicity/tolerability and burden perspective, and what is the real need for dosing. Three weeks [was the initial design, and there are many] studies going on trying to figure out how we can spread that out....Missed doses in between don’t impact the long-term control. That 6 weeks makes life a lot easier for patients; it gets them to eye doctors less frequently, adverse events [AEs] tend to be a little better. It is something we have to keep an eye on.

PARRONDO: Have you combined it with anything?

SHAIN: I have not done it with anything else, and generally I’ve been holding it for [patients] who are a little later in disease state than it was approved for. Most of the belantamab mafodotin I’ve recommended is to my colleagues in the community because we have trials here, and I think it’s a little easier for patients that way, so they’re not traveling back and forth. I haven’t tried to push hard.

There are...nice combination data we’ll be learning more about. Pomalidomide [plus carfilzomib] is one of the combinations, as well as other agents we have going on....There’s going to be a move toward how to better blend [belantamab] with our current therapies, without question.

DISCUSSION QUESTIONS

• Have you used selinexor/dexamethasone?
• What are your experiences or perceptions of this combination?
THE FIRST EVER TARGETED THERAPY FOR RESECTABLE EGFRm NSCLC

The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients\(^1\)\(^-\)\(^3\)

**PRIMARY ENDPOINT: DISEASE-FREE SURVIVAL IN PATIENTS WITH STAGE II/IIIA DISEASE (N=470)**

![Graph showing disease-free survival rates](image)

- **1-year DFS rate**
  - TAGRISSO: 97%
  - Control arm: 61%
- **2-year DFS rate**
  - TAGRISSO: 90%
  - Control arm: 44%
- **3-year DFS rate**
  - TAGRISSO: 78%
  - Control arm: 28%

**83% REDUCTION IN RISK OF RECURRENCE OR DEATH**

**HR=0.17 (95% CI: 0.12, 0.23), P<0.0001**

Consistent results with or without prior adjuvant chemotherapy\(^2\)\(^-\)\(^3\)

- Patients in the ADAURA trial are treated with **ORAL TAGRISSO FOR 3 YEARS** or until disease recurrence or unacceptable toxicity\(^3\)

\(^1\)Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.\(^1\)

\(^2\)Control arm=placebo.

\(^3\)Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.16 (95% CI: 0.10, 0.26) and for patients without adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).\(^2\)

Indication

- TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

Select Safety Information

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

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ADAURA study design: Phase III, double-blind, randomized, placebo-controlled trial in 682 patients with completely resected stage IB, II, and IIIA NSCLC with or without adjuvant chemotherapy. NSCLC patients had centrally confirmed EGFR mutations (exon 19 deletion or L858R mutation). Patients were stratified by stage (IB vs II vs IIIA), EGFR mutation (exon 19 deletion or L858R), and race (Asian vs non-Asian). Patients were randomized to either TAGRISSO (n=339, 80 mg orally, once daily) or placebo (n=343). The maximum interval between surgery and randomization was 26 weeks with adjuvant chemotherapy and 10 weeks without adjuvant chemotherapy. The primary endpoint of the study was DFS by investigator assessment in stage II/IIIA patients. The secondary endpoints were DFS in the overall population (stage IB/II/IIIA); DFS rate at 2, 3, 4, and 5 years; overall survival (stage II/IIIA and overall population); safety, and health-related QoL. The planned treatment duration was 3 years or until disease recurrence/unacceptable toxicity.1,2

**TAGRISSO® (osimertinib) tablets, for oral use**

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

**INDICATIONS AND USAGE**

Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

**First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC**

TAGRISSO is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

**Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC**

TAGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test.

**Dosage and Administration**

**Patient Selection**

Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens.

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens (see Clinical Studies [14] in the full Prescribing Information). If these mutations are not detected in a plasma specimen, test tumor tissue or fluid for these mutations.

Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TAGRISSO following progression on or after prior EGFR TKI therapy based on the presence of an EGFR T790M mutation in tumor or plasma specimens (see Clinical Studies [14] in the full Prescribing Information). Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.

Information on FDA-approved tests for the detection of EGFR mutations is available at www.fda.gov/companiondiagnostics.

**Recommended Dosage Regimen**

The recommended dosage of TAGRISSO is 80 mg tablet once a day. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

 Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity, or for up to 3 years.

 Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.

 **Administration to Patients Who Have Difficulty Swallowing Solids**

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 5 mL of non-carbonated water and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered per nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

**Dosage Modifications**

**Table 1. Recommended Dosage Modifications for TAGRISSO (cont’d)**

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction *</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (see Warnings and Precautions [5.1] in the full Prescribing Information)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal lung disease (ILD)/Pneumonitis</td>
<td></td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

**QTc Interval**

<table>
<thead>
<tr>
<th>QTc Interval greater than 500 msec on at least 2 separate ECGs†</th>
<th>Withhold TAGRISSO until QTc interval is less than 500 msec.</th>
<th>Permanently discontinue TAGRISSO.</th>
</tr>
</thead>
</table>

**Symptomatic congestive heart failure**

Withhold TAGRISSO if suspected and permanently discontinue if confirmed.

**CUTANEOUS (see Warnings and Precautions [5.5] in the full Prescribing Information)**

- Stevens-Johnson syndrome (SJS), Erythema Multiforme Major (EMM)

- If QTc interval is greater than 500 msec, continue TAGRISSO at 40 mg daily.

**Other [see Adverse Reactions (6.1) in the full Prescribing Information]**

- If QTc interval is greater than 500 msec, continue TAGRISSO at 40 mg daily.

**QTc Interval Prolongation**

Heart rate-corrected QTc (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1479 TAGRISSO-treated patients, 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Permanently discontinue TAGRISSO if ILD is confirmed (see Dosage and Administration [2.4] and Adverse Reactions [6] in the full Prescribing Information).

**Cardiac Tests**

- Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO (see Dosage and Administration [2.4] in the full Prescribing Information).

**Keratitis**

Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

**Erythema Multiforme and Stevens-Johnson Syndrome**

Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

**Cutaneous Vasculitis**

Postmarketing cases of cutaneous vasculitides including leukocytoclastic vasculitis, urticarial vasculitis, and γδ T-cell vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.

**Embyro-Fetal Toxicity**

Based on animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose 1.5 times the exposure at the maximum recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females to be treated with TAGRISSO prior to initiating therapy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose (see Use in Specific Populations [8.1, 8.3] in the full Prescribing Information).

**Adverse Reactions**

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

- Interstitial Lung Disease/Pneumonitis (see Warnings and Precautions [5.1] in the full Prescribing Information)
- QTc Interval Prolongation (see Warnings and Precautions [5.2] in the full Prescribing Information)
- Cardiomyopathy (see Warnings and Precautions [5.3] in the full Prescribing Information)
- Keratitis (see Warnings and Precautions [5.4] in the full Prescribing Information)
- Erythema multiforme and Stevens-Johnson syndrome (see Warnings and Precautions [5.5] in the full Prescribing Information)
- Cutaneous Vasculitis (see Warnings and Precautions [5.6] in the full Prescribing Information)

**Clinical Trials Experience**

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

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials (ADAURA [n=337], FLAURA [n=279], and AURA3 [n=279]), two single arm trials (AURA Extension [n=201] and AURA2 [n=210]), and one dose-finding study, AURA1 (n=173) [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) [see Warnings and Precautions (5) in the full Prescribing Information].

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥10 percentage points from baseline and to less than 50% LVEF occurred in ≥2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (S252) of patients treated with TAGRISSO experienced LVEF decrease greater than or equal to 10 percentage points and a drop to less than 50%.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or
Adjuvant Treatment of EGFR Mutation-Positive NSCLC

The safety of TAGRISSO was evaluated in ADAURA, a randomized, double-blind, placebo-controlled trial for the adjuvant treatment of patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 22.5 months.

Serious adverse reactions were reported in 16% of patients treated with TAGRISSO. The most common serious adverse reaction (≥1%) was pneumonia (1.5%). Adverse reactions leading to dose reductions occurred in 9% of patients treated with TAGRISSO.

The most frequent adverse reactions leading to discontinuation of treatment were diarrhea (4.5%), stomatitis (3.9%), nausea (3.3%), rash (1.8%) and headache (1.8%). Adverse reactions leading to permanent discontinuation occurred in 4% of patients treated with TAGRISSO.

The most frequent adverse reactions leading to discontinuation of TGRARSE were interstitial lung disease (2.7%), rash (1.2%) and fatigue (1.2%).

Table 2 summarizes common adverse reactions and laboratory abnormalities which occurred in ADAURA.

### Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in ADAURA.

### Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TGRARSE in ADAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TGRARSE (%337)</th>
<th>PLACEBO (%343)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>47.4</td>
<td>20.3</td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>32.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Abdominal Pain**</td>
<td>12.7</td>
<td>7.0</td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash‡</td>
<td>40.6</td>
<td>19.0</td>
</tr>
<tr>
<td>Nail toxicity§</td>
<td>37.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Dry skin¶</td>
<td>29.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>19.0</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>19.0</td>
<td>19.0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain ‡‡</td>
<td>18.3</td>
<td>25.3</td>
</tr>
<tr>
<td><strong>Infection and Infestation Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis 14.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection 13.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection 10.0</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue 13.6</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness 10.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite 13.6</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>

* No CTC AE v4.0
† Includes diarrhea, colitis, enterocolitis, enteritis.
‡ Includes aphthous ulcer, oral ulceration, glossitis, tongue ulceration, stomatitis and mouth ulceration.
§ Includes abdominal discomfort, abdominal pain, abdominal lower pain, abdominal upper pain, abdominal discomfort, hepatic pain.
¶ Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash purpuric, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, eczema asthmaticum, lichen planus, skin erosion, pustular.
†† Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onycholysis, onychocytosis, onychoschizia, onychodystrophy, onychomadesis, onychotony.
‡‡ Includes dry skin, skin fissures, xerosis, xeroderma.
§§ Includes pruritus, pruritus generalized, eyelid pruritus.
** Includes urticaria, arthralgia, back pain, bone pain, muscle pain, musculoskeletal chest pain, muscle pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity.
‖ Includes cystitis, urinary tract infection, and urinary tract infection bacterial.
¶¶ Includes asthma, fatique.
#### Clinically relevant adverse reactions in ADAURA in <10% of patients receiving TGRARSE were alopecia (6%), epistaxis (6%), interstitial lung disease (3%), palmar-plantar erythrodysesthesia syndrome (1.8%), urticaria (1.5%), keratitis (0.6%), QTc interval prolongation (0.6%), and erythema multiforme (0.3%). QTc interval prolongation represents the incidence of patients who had a QTc prolongation >500msec.

### Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TGRARSE (N=337)</th>
<th>PLACEBO (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia 54.0</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia 47.0</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia 44.0</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>Anemia 30.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia 25.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
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<td></td>
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<tr>
<td>Hyperglycemia 25.0</td>
<td>30.0</td>
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</tr>
<tr>
<td>Hyperlipidemia 18.0</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td><strong>Prolonged QT Interval</strong></td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td><strong>Infection and Infestation Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough 12.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain 16.0</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td><strong>Infection and Infestation Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection or Infestation Disorders 14.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>**Upper respiratory tract infection 13.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>**Urinary Tract Infection 10.0</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue 14.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness 10.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite 13.6</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>

* NCI CTCAE v4.0
† Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. NCI CTCAE range: 267 - 273 and EGFR TKI comparator range: 256 - 266.
‡ Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TGRARSE (179) and EGFR comparator (191).

Clinically relevant laboratory abnormalities in FLAURA that occurred in ≥20% of patients receiving TGRARSE were thyrotoxicosis (6%), lymphocytosis, lymphopenia (2.2%), palmar-plantar erythrodysesthesia syndrome (1.4%), increased blood creatinine (1.1%), and keratitis (0.4%). QTc interval prolongation represents the incidence of patients who had a QTc prolongation >500msec.

### Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TGRARSE in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TGRARSE (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea1 58.1</td>
<td>57.2</td>
<td></td>
</tr>
<tr>
<td>Stomatitis1 32.0</td>
<td>22.1</td>
<td></td>
</tr>
<tr>
<td>Nausea 14.0</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>Constipation 15.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Vomiting 11.0</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash‡ 58.1</td>
<td>78.7</td>
<td></td>
</tr>
<tr>
<td>Dry skin§ 36.0</td>
<td>36.1</td>
<td></td>
</tr>
<tr>
<td>Nail toxicity§ 35.0</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>Pruritus† 17.0</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue* 21.0</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>Pyrexia 10.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite 20.0</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough 17.0</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>Dyspnea 13.0</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache 12.0</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>

* NCI CTCAE v4.0
† Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. NCI CTCAE range: 267 - 273 and EGFR TKI comparator range: 256 - 266.
‡ Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TGRARSE (179) and EGFR comparator (191).
chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 (58%), female (64%), Asian (65%), never smokers (88%), and EGFR PS 0 or 1 (100%). Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 26% in the chemotherapeutic group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Table 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3.

### Table 6. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>16.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>19.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>34.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Dry skin†</td>
<td>23.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Nail toxicity‡</td>
<td>22.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>12.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* No CI/CTCAE v4.0
† No grade 4 events were reported.
‡ Includes stomatitis and mouth ulceration.

### Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3 (cont’d)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAGRISSO (N=279)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43.0 0.0</td>
<td>29.9 17.8</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63.8 0.0</td>
<td>61.0 10.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46.7 0.0</td>
<td>48.7 7.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27.2 0.0</td>
<td>49.1 12.0</td>
</tr>
</tbody>
</table>

† Includes hyperglycemia, based on the number of patients with both baseline and at least one on-study laboratory measurement available (TAGRISSO 279, Chemotherapy comparator 121).
‡ Includes skin and subcutaneous tissue: Stevens-Johnson syndrome, erythema multiforme, cutaneous vasculitis.

### Drug Interactions

**Effect of Other Drugs on Osimertinib**

**Strong CYP3A4 Inducers**

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone (see Clinical Pharmacology (12.3) in the full Prescribing Information). Decreased osimertinib exposure may lead to reduced efficacy. Avoid co-administering TAGRISSO with strong CYP3A4 inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable (see Dosage and Administration (2.4) in the full Prescribing Information). No dose adjustments are required when TAGRISSO is used with moderate or weak CYP3A4 inducers.

**Effect of Osimertinib on Other Drugs**

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone (see Clinical Pharmacology (12.3) in the full Prescribing Information). Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

**Drugs That Prolong the QT Interval**

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering drugs known to prolong the QTc interval with TAGRISSO. The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering drugs known to prolong the QTc interval with TAGRISSO. The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering drugs known to prolong the QTc interval with TAGRISSO.

**Use in Specific Populations**

**Pregnancy**

Risk Summary

Based on data from animal studies and its mechanism of action (see Clinical Pharmacology (12.1) in the full Prescribing Information), TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose (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

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from gestation days 6 to 10 at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

**Lactation**

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death [see Use in Specific Populations (8.1) in the full Prescribing Information]. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

**Females and Males of Reproductive Potential**

Based on animal data, TAGRISSO can cause malformations, embryo lethality, and postnatal death at doses resulting in exposures 1.5 times or less the human exposure at the clinical dose of 80 mg daily [see Use in Specific Populations (8.1) in the full Prescribing Information].

**Pregnancy Testing**

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

**Contraception**

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose [see Use in Specific Populations (8.1) in the full Prescribing Information].

**Males**

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO [see Nonclinical Toxicology (13.1) in the full Prescribing Information].

**Infertility**

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible [see Nonclinical Toxicology (13.1) in the full Prescribing Information].

**Pediatric Use**

No data on the safety and effectiveness of TAGRISSO in pediatric patients have not been established.

**Geriatric Use**

Forty-three percent (43%) of the 1479 patients in AURA4 (n=537), FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURAl1 (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (35% vs 27%) and more frequent dose modifications for adverse reactions (32% vs 21%) in patients 65 years or older as compared to those younger than 65 years.

**Renal Impairment**

No dose adjustment is recommended in patients with creatinine clearance (CLcr) 15 - 89 ml/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr <15 ml/min) [see Clinical Pharmacology (12.3) in the full Prescribing Information].

**Hepatic Impairment**

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST ≤ ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin ≥ 3 to 10 times ULN and any AST) [see Clinical Pharmacology (12.3) in the full Prescribing Information].

**Drug Interactions**

The effect of con-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering drugs known to prolong the QTc interval with TAGRISSO. The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering drugs known to prolong the QTc interval with TAGRISSO. The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering drugs known to prolong the QTc interval with TAGRISSO.
MALHOTRA: I’ve used it in 1 patient. He had relapsed [multiple times] and was not a candidate for transplant. CAR T was not an option until a while ago. Diarrhea was the main challenge, and then fatigue. He seemed to get benefit for maybe 3 months [with selinexor/dexamethasone]; it was not a dramatic response, and he subsequently passed on.

GREENBERG: Right now, I don’t use the doublet—I use the triplet with bortezomib, selinexor, and dexamethasone, which I find is much better tolerated using selinexor once rather than twice weekly, and the bortezomib once weekly. I’ve seen, [in] my limited experience, longer responses with the triplet than with the doublet, and less gastrointestinal toxicity.

SHAIN: That’s a very good point. To add onto that, we did a lot with selinexor...as a single agent, then going to doublet. I think triplets, and the correct lower dosing [or] weekly dosing, is the only way we’re going to keep patients on it long term without too much toxicity.

NAKKA: I have 2 patients on selinexor. The most significant [AE] in both...was fatigue, just not able to get out and do what they wanted to do. They’re still continuing [but] it’s a whole lot of fatigue.

SHAIN: Have you dropped the dose significantly for them?

NAKKA: No, and [I give it] once a week.

SHAIN: Sometimes lower doses make [patients] feel a lot better. Nausea, vomiting, fatigue, diarrhea—those are things you have to battle. Cytopenias seem to get a little better after the first cycle....It’s something we all [must] think about, but using it in triplet seemed in my experience as well to give us a much better feel for our ability to drop the dose a bit, and you still maintain that activity.

AMIN: I used [the regimen] in a patient but it was late, based on the STOMP data with the selinexor and carfilzomib [NCT02343042]. But it was late-stage disease and the patient progressed through multiple lines. I didn’t get much response. I have used the regimen in the BOSTON trial [NCT03110562], and the patient had CR in that time.

I’m using it more and in an earlier line as a combination with bortezomib or, if the insurance allows it, I try to use it with pomalidomide or carfilzomib.

PARRONDO: I usually give Zyprexa [olanzapine] when I give [selinexor], and that helps with the nausea.

SHAIN: That’s what I do as a rule....Zyprexa [or] Zofran [ondansetron] at home, make sure they have lots of Imodium [loperamide], and call us with other things they need for the other side. Nausea has always been my biggest concern with this. The lower doses make it a little easier; usually you can tweak it to find the right place.

AMIN: That’s very interesting, because when I had a patient back...when the BOSTON trial started. The patient did not have any [AEs]. The patient was on an antipsychotic drug for psychiatric reasons. I don’t know if that prevented nausea or did not.

DISCUSSION QUESTIONS

• How familiar are you with keratopathy?
• With its management?
• Have you had to interact with any of your patients’ eye care providers (eg, ophthalmologist)?
• What support services/resources have you found helpful for patients with ocular toxicities?

PARRONDO: At Mayo Clinic [in Jacksonville, Florida], we’re pretty good about getting them to see the ophthalmologist. [The ophthalmologist] basically writes a note with an eye exam; they don’t even really grade it. I have to read their note and determine the grade. That information is helpful so I can put it into REMS so they can release the note. The REMS booklet [for belantamab] is helpful. It has a table that tells you exactly what to do. With grade 1, you keep going at the same dose and interval. With grade 2, you’re supposed to hold it until the keratopathy resolves to grade 1. Anything above grade 3 or grade 4, you’re supposed to hold and reduce the dose when you restart. →
**SHAIN:** We have someone who is local. At the University of South Florida [Morsani College of Medicine]...we see [the patient] and we email back and forth; it’s an easy communication. It’s been great. That’s something that’s been set up, so I would be curious about how it’s worked in the community and what are the obstacles? How has it worked out for those who’ve used this?

**MALHOTRA:** One of my local ophthalmologists... called me and said he had seen some cases—one of my colleague’s patients—and he said he’s gotten up to speed on it. He said if I had any patients, he was happy to get them in right away and take care of them, and...monitor. I felt encouraged; that’s a big hurdle for us, so I do have in my community an ophthalmologist who’s willing and keen to do it, and so I’m more encouraged to use it.

**AMIN:** For one of my first cases, I had to talk with [the ophthalmologist] a while to explain to him the grading system. Eventually, in subsequent cases, it was helpful. I’ve been using him for a while now, and I have a trial also, so it was protocol-driven; a lot of education was given to him in terms of the grading system. But I still have a talk with [him about] every case after his report, because there is some confusion about how he grades and what he sees. It’s not clear yet, but I’m sure as the time goes [on] we’ll get there.

**SHAIN:** In theory, GlaxoSmithKline is able to help find those individuals in the community for you and help try to educate them to help the communication process. That is something to think about, if you haven’t done so. [If you’re thinking about using belantamab, there is help, so your representative should be able to help you from that perspective.]

How resistant have your patients been to this additional step? My biggest hurdle is patients [being resistant to going to an ophthalmologist or optometrist], more than anything else. If I give someone 2 options, they’re almost unanimously going to take an option that doesn’t involve seeing another physician. How have you dealt with that, or are your patients [ready to do it]?

**DANDAMUDI:** Especially because this is after 4 lines of treatment, if the patient performance status is good, usually they agree to see the ophthalmologist and follow up regularly...At the same time, if the performance status is going down, that is a difficult situation. They don’t want to travel from one clinic to another. That’s a big problem in the community setting.

**SHAIN:** I’ve been surprised by the steadfastness of the patients. I consider myself pretty good at trying to sell a regimen, so it’s interesting. Maybe it’s just the last couple, but it stuck in me.

---

**CASE UPDATE**

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

**DISCUSSION QUESTION**

How do you see belantamab mafodotin fitting into the overall treatment plan for relapsed/refractory multiple myeloma?

**GREENBERG:** I think now, with the availability of CAR T-cell therapies, belantamab is probably going to be pushed back...further, maybe 1 or 2 lines after getting CAR T-cell therapy. I think there are multiple options until that point.

**NAHAS:** There are clever ways to use these agents, and maybe even in combination with other drugs. But I agree that with some of these other BCMAs, which objectively have...good ORRs and CR rates, I probably would go after those for a regimen as opposed to this antibody-drug conjugate. But I don’t know; it’s hard to say, especially with CAR.

With CAR Ts, the waiting time and the slot time are very difficult, but...it will be interesting to see what happens to something like belantamab in the setting of BiTEs, which [are hopefully] going to have a nice ORR, nice numbers, in the setting of being essentially an off-the-shelf agent for us.

**SHAIN:** Absolutely. That’s a truly exciting group of agents there.

**MALHOTRA:** In patients who are multiply relapsed/refractory, and the fact that these are non-cross-resistant,
usually, to the other drugs we use, they are very useful additions. I think this discussion helps me lower my barriers to [using belantamab]—hearing other [doctors’ experiences], getting your insights into it. I’ll be more open to using it in the right patient.

**SHAIN:** [When] we have these agents, you’re going to find a patient for everything. Every patient’s going to need everything you can think of, is my way of looking at it. How you are going to sequence those drugs, where you are going to use them, and how you are going to introduce them are really the critical part. Learning about them is the first step in how you get your patients the right drugs at the right time.

**DANDAMUDI:** One thing that I learned is those patients who respond [to belantamab] may respond for a long time, so that’s the key. We can encourage the patient to use that, and after 1 or 2 cycles, if he doesn’t respond we can move on. But those [individuals] who respond, we can intermittently dose the patient.

**CASTANEDA:** We are seeing, or we are even recommending in some patients to use belantamab as a bridge to CAR even though there is no patient with prior BCMA therapy on...the ciltacabtagene autoleucel trials. But it’s not a contraindication, if that’s the only thing that the patient may have for bridging. That’s also something that you should keep in mind in case you are thinking about what else [to use] to bridge this patient to CAR....That’s still a reasonable option.

The word out on the street is that patients are still responding. We are going to narrow this with real-world data that will be coming out from those experiences, and for what we are doing.

**REFERENCES**


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Hanna Discusses Efficacy Results of Different Treatments in RET-Positive Lung Cancer

**CASE**

- A 59-year-old man presented with dyspnea on exertion, fatigue, anorexia, and a 5-lb weight loss.
- Prior medical history: diabetes mellitus, medically controlled
- Smoking history: nonsmoker
- Physical exam: thin-appearing man
- Labs: Within normal limits

**Imaging:**
- Chest x-ray showed 2 right lower lobe masses.
- Chest/abdomen/pelvic CT scan confirmed 2 masses (4.7 cm and 7.4 cm) in right lower lobe of lung.
- PET scan showed activity in the right lower lobe masses.
- MRI of the brain showed 3 small lesions; consistent with brain metastases.
- Bronchoscopy with transbronchial biopsy of the right lower lobe confirmed lung adenocarcinoma; PD-L1 80%.
- Staging: IVA adenocarcinoma; ECOG performance status: 1
- Patient has no central nervous system (CNS) symptoms.

**Targeted Oncology™:** What do the National Comprehensive Cancer Network (NCCN) guidelines say, and what drives your selection of a RET inhibitor in the front line?

**HANNA:** You want to use selpercatinib [Retevmo] or pralsetinib [Gavreto] as first-line therapy if you know the patient has a RET fusion.¹ The question is: What if you started them on treatment and then found out they had a RET fusion? The NCCN says you should complete [the treatment you’re] already doing, including giving a maintenance therapy, if you see they are benefitting from the treatment. I have a low threshold to quit on it, but if somebody is responding and tolerating well, it’s not unreasonable to continue to treat them with the drugs that are tolerable and working. However, you should quickly follow that with either selpercatinib or pralsetinib at the earliest sign that you need to do something differently.

The ARROW trial [NCT03037385] with pralsetinib had a phase 1 that went into a phase 2 dose expansion looking at response rates and safety.² This trial had 2 cohorts; those who had received platinum therapy and those who were treatment naïve. With pralsetinib, [up to] 40% had central nervous system [CNS] metastases—either current or a prior history of—and you can see the KIF5B is the most common fusion partner.²,³

The overall response rate [ORR] in the treatment-naïve group was 70%, and in the previously treated group with platinum, it was 57%. A little lower activity for pralsetinib in the previously treated group. With pralsetinib and some combined data sets, there was a 62% response rate with prior treatment and a 79% response rate in the treatment-naïve group, and the studies underwent a revision for the treatment-naïve group.

Originally, you could not be eligible for chemotherapy, then they revised it and said [that], yes, even those who are eligible for chemotherapy can go on it. When they looked at the treatment-naïve group and that expanded cohort of patients who were more fit and chemo-appropriate, the response rate went up to 88%. There was a small subset of patients with brain metastases, and of these patients, 4 of the 8 with brain metastases had a response in the brain, usually durable.

There are a couple of adverse events [AEs] I want to point out: No. 1 being hypertension [and the second being] pneumonitis. You [must] pay attention to

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pneumonitis because 10% of patients do get pneumonitis, although it’s usually grade 1 or 2.3 Pneumonitis is associated with pralsetinib. It’s not associated with selpercatinib, but hypertension is also a class feature.3,4 Transamnainase elevations also occur, although they’re usually grade 1, and you can get a little bit of hematologic toxicity that is usually grade 1.3 You can get a little bit of lymphopenia, but it’s usually not clinically significant. Pralsetinib was also recently FDA approved if the patient had a RET gene fusion in their lung cancer.5

The LIBRETTO-001 trial [NCT03157128] data with selpercatinib [were] in [patients with] RET fusion–positive non–small cell lung cancer [NSCLC], both treatment-naïve and previously treated cohorts.6, 7 It had a phase 1 study, which led into a phase 2 dose escalation study. The important take-home messages [are] that [approximately] 70% of these patients were never smokers and almost all of them have adenocarcinoma. In the previously treated group, 36% had CNS metastases, and the most common fusion partners were KIF5B, once again.

**POLLING QUESTION**

At a live virtual event, Hanna asked participants, “What systemic therapy are you most likely to offer this patient with RET-rearranged, PD-L1–high metastatic NSCLC?”

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<th>Therapy</th>
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<tr>
<td>RET inhibitor</td>
<td>92%</td>
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<td>Chemotherapy + immune checkpoint inhibition (ICI)</td>
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<td>VEGF tyrosine kinase inhibitor (eg, cabozantinib, vandetanib)</td>
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**TOTAL VOTES: 12**

Were the patients in the ARROW and LIBRETTO trials treated with radiation, or were they just started on the RET inhibitors?

Some of them were not treated. Some of them were allowed to go to the tyrosine kinase inhibitor [TKI] without treatment, [as long as they were asymptomatic].6,7 I typically extrapolate from the data we know with EGFR and ALK, where we have huge robust data sets, and those studies show that you should consider doing gamma knife or stereotactic radiation to the brain metastases.

Of course, it can be limited to the number, size, and location, plus giving the TKI. But doing just the TKI is not as good for long-term CNS control, and you should largely avoid whole-brain radiation unless you absolutely can’t avoid it. Most of these studies do not show that you improve outcomes by giving these patients whole-brain radiation. I do quite a bit of stereotactic radiosurgery, as well as giving the TKIs. If they’re very small brain metastases, I just give the TKI and observe, but if they’re a bit larger brain metastases, I tend to use Gamma Knife for the more symptomatic larger ones. Now in the treatment-naïve group of the LIBRETTO trial, the response rate is 85% and the disease control rate overall is 94%.6,7

The evaluation of the patients with CNS metastases had a sample size of 22 patients, so more than the 8 patients with pralsetinib. You can also see 8 of those patients had brain radiation, whereas the other 14 did not. The objective response rate in the brain was 82%, so again, higher than pralsetinib, but I wouldn’t read too much into that. Pretty much every patient got an objective response in the brain, and those patients did have some prior therapy.

In terms of adverse reactions, hypertension is a class effect, as is elevation of liver enzymes [and] transaminits, so that is a class effect.6,7 You do get a little bit of peripheral edema with selpercatinib, as well. You get that with other drugs; the MET inhibitors are notorious for peripheral edema. There [were] very few grade 3 or 4 adverse reactions [with selpercatinib]. There can be pyrexia, a little bit of QTc prolongation, and a little bit of rash.8 [Earlier in 2020], the FDA approved this treatment for patients with RET-mutated or -fused disease and for [patients with] lung and thyroid cancers, as well.9

As a summary, pralsetinib is [administered] once per day, and selpercatinib is [administered] twice per day.3,4 Pneumonitis is a risk with pralsetinib, but you see hypertension in both [as well as] some transaminits in both. The response rates were 80% to 85% in the untreated group, and [approximately] 60% in the previously treated group, with high CNS response rates.

What do the NCCN guidelines say, and what are the data for therapy in patients who have an ALK fusion in the frontline setting?

According to the NCCN guidelines, if you know the patient has an ALK fusion, they prefer alectinib [Alencena], brigatinib [Alunbrig], or lorlatinib [Lorbrena].1 If you are already treating them and then discover they have an ALK fusion, then it’s the same story as RET. [So it is] reasonable to continue what you’re already doing, including maintenance—perhaps maybe pemetrexed [Alimta]—but [if there are] any signs of toxicity or of treatment failure, [there should be a quick switch] to any one of those drugs.

[There are various] ALK inhibitors, such as crizotinib [Xalkori], ceritinib [Zykadia], alectinib, brigatinib, and lorlatinib. The latter 3 are preferred first-line drugs.1 Both crizotinib and ceritinib have been compared head-to-head [with] platinum/pemetrexed, and both had substantially better response rates and PFS [progression-free survival].10,11

continued on page 71
ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status.

Indication

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Important Safety Information

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1,785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≥Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reconnecting ZEJULA is unknown.

Embryo-fetal toxicity and lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.
resolve within 28 days following interruption, discontinue ZEJULA, and complete blood counts weekly for the first month, monthly for the next ≤ of patients. Do not start ZEJULA until patients have recovered from anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% patients receiving ZEJULA. Discontinuation due to thrombocytopenia, baseline weight or platelet count, Grade In patients who were administered a starting dose of ZEJULA based on 3, 2%, and 2% of patients. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. PRIMA, the overall incidence of Grade Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. In patients with cardiovascular disorders, especially coronary insufficiency, periodically thereafter during treatment with ZEJULA. Closely monitor also been described in postmarketing reports. Monitor all patients for associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer steroid treatment and/or fluid replacement therapy. Discontinue ZEJULA if hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Important Safety Information (continued)

Allergic reactions to FD&C Yellow No. 5 (tartrazine): ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

The most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%), and increased ALT (29%).

Please see Brief Summary on the following pages.


Visit ZEJULAHCP.COM to explore the PRIMA data

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Produced in USA.
1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer
ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer
ZEJULA is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies
ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more chemotherapies. A diagnosis of homologous recombination deficiency (HRD) is not a positive test for homologous recombination deficiency. Homologous recombination deficiency is associated with homologous recombination deficiency (HRD) positive status defined by either:
- A deleterious or suspected deleterious BRCA mutation, or
- Genomic instability and who have progressed more than 5 months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia
Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received monotherapy with ZEJULA in clinical trials. In a LBRIR patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZEJULA in patients who developed secondary MDS/AML therapy-related AML varied from 0.5 months to 4.9 years. All of these patients had received previous chemotherapy with platinum and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression
Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or pancytopenia have been reported in patients treated with ZEJULA (see Adverse Reactions (6.1)).

In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 36%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 25% and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

In NOVA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 1%, and 2%, respectively, of patients.

In QUADRA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 28%, 27%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients. Do not start ZEJULA until patients have recovered from hematologic toxicity caused by previous chemotherapy (≥Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) of full prescribing information).

5.3 Hypertension and Cardiovascular Effects
Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA in clinical trials.

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 551 days) and with a median duration of 12 days (range: 1 to 161 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 80 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRA, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter in patients treated with ZEJULA. Consider a starting dose of ZEJULA based on baseline weight or platelet count, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA in the NOVA trial and not included in the table: tachycardia, headache (23%), dizziness (14%), acute kidney injury (13%), urinary tract infection (2%), and hypomagnesemia (1%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer
The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.1 to 29 months).

All Patients Receiving ZEJULA in PRIMA: Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (16%), anemia (6%), and neutropenia (5%). Fetal and neonatal deaths occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1% each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZEJULA included thrombocytopenia (3%), anemia (1.9%), and nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

Table 1 and Table 2 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in all patients treated with ZEJULA in the PRIMA study.

Table 1: Adverse Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 1-4 (%)</th>
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<tbody>
<tr>
<td>ZEJULA</td>
<td>Placebo</td>
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<td>Fatigue</td>
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Ovarian, fallopian tube, or primary peritoneal cancer who have been ZEJULA is indicated for the treatment of adult patients with advanced cancer who are in a complete or partial response to platinum-based maintenance treatment of recurrent ovarian cancer. Patients receiving ZEJULA with dose based on baseline weight or platelet count in PRIMA. Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months range, 1 day to 16 months. Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%). Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA.

Table 3: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=484)</th>
<th>Placebo (n=484)</th>
<th>ZEJULA (n=244)</th>
<th>Placebo (n=244)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>53 (21)</td>
<td>1 (0)</td>
<td>50 (23)</td>
<td>12 (5)</td>
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<tr>
<td>Constipation</td>
<td>31 (13)</td>
<td>1 (0)</td>
<td>21 (8)</td>
<td>1 (0)</td>
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<tr>
<td>Vomiting</td>
<td>17 (7)</td>
<td>1 (0)</td>
<td>27 (11)</td>
<td>1 (0)</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48 (20)</td>
<td>4 (1)</td>
<td>28 (11)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

The following adverse reactions and laboratory abnormalities have been identified in ≥1% to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypoalimentation, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, and epistaxis.

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 65% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days. Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

Table 5: Adverse Reactions Reported in ≥1% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=367)</th>
<th>Placebo (n=367)</th>
<th>ZEJULA (n=179)</th>
<th>Placebo (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>34 (4)</td>
<td>4 (1)</td>
<td>15 (8)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>21 (6)</td>
<td>1 (0)</td>
<td>17 (9)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (3)</td>
<td>1 (0)</td>
<td>7 (4)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (4)</td>
<td>1 (0)</td>
<td>10 (5)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (3)</td>
<td>1 (0)</td>
<td>7 (4)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (4)</td>
<td>1 (0)</td>
<td>13 (7)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 (6)</td>
<td>1 (0)</td>
<td>12 (6)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (5)</td>
<td>1 (0)</td>
<td>4 (2)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>ZEJULA (n=484)</th>
<th>Placebo (n=484)</th>
<th>ZEJULA (n=244)</th>
<th>Placebo (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>87 (66)</td>
<td>29 (1)</td>
<td>81 (60)</td>
<td>21 (0)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>74 (33)</td>
<td>17 (7)</td>
<td>70 (28)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>71 (36)</td>
<td>9 (0)</td>
<td>63 (26)</td>
<td>10 (0)</td>
</tr>
<tr>
<td>Glucose</td>
<td>66 (57)</td>
<td>3 (0)</td>
<td>56 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>51 (29)</td>
<td>7 (3)</td>
<td>40 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>46 (26)</td>
<td>1 (0)</td>
<td>33 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>40 (23)</td>
<td>0 (0)</td>
<td>37 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>36 (20)</td>
<td>1 (0)</td>
<td>29 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>35 (20)</td>
<td>1 (0)</td>
<td>21 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>29 (16)</td>
<td>2 (1)</td>
<td>15 (6)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>21 (11)</td>
<td>1 (0)</td>
<td>15 (6)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>15 (9)</td>
<td>0 (0)</td>
<td>11 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>11 (6)</td>
<td>0 (0)</td>
<td>7 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>5 (3)</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Common Terminology Criteria for Adverse Events version 4.02.

*Includes preferred terms of neuropenic infection, neutropenic sepsis, and febrile neutropenia.

Table 7: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=367)</th>
<th>Placebo (n=367)</th>
<th>ZEJULA (n=179)</th>
<th>Placebo (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>85 (26)</td>
<td>18 (6)</td>
<td>49 (27)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>72 (21)</td>
<td>4 (1)</td>
<td>32 (18)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>66 (20)</td>
<td>2 (1)</td>
<td>29 (16)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53 (15)</td>
<td>5 (3)</td>
<td>25 (14)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>36 (10)</td>
<td>2 (1)</td>
<td>17 (10)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

...continued on next page...
Anemia includes events with preferred terms of anemia, hemoglobin
Common Terminology Criteria for Adverse Events version 4.02.
AST/ALT = Aspartate transaminase/alanine aminotransferase.
normocytic anemia.
neutrophil count decreased, neutropenic infection, and neutropenic
ZEJULA in QUADRA
Cough 13 0
Acute kidney injury 17 1
Insomnia 21 1
Dizziness 11 0
Urinary tract infection 15 2
Infections and infestations

Neutropenia

General disorders and administration site conditions

Nervous system disorders

Musculoskeletal and connective tissue disorders

Musculoskeletal pain

Nervous system disorders

Headache 19 0.4
Dizziness 11 0
Psychiatric disorders

Insomnia 21 1
Renal and urinary disorders

Acute kidney injury 17 1
Respiratory, thoracic and mediastinal disorders

Dyspnea 22 3
Cough 13 0
Vascular disorders

Hypertension 14 5

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ZEJULA. 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.

Blood and lymphatic system disorders

Anemia¹

Thrombocytopenia¹

Neutropenia²

Gastrointestinal disorders

Nausea 57 10
Vomiting 44 8
Constipation 36 5
Abdominal pain 34 7
Diarrhea 17 0.2

General disorders and administration site conditions

Fatigue 56 7

Infections and infestations

Urinary tract infection 26 2

Investigations

Blood alkaline phosphatase increased 11 2
AST/ALT elevation 11 1

Metabolism and nutrition disorders

Decreased appetite 27 2

Musculoskeletal and connective tissue disorders

Musculoskeletal pain 29 3

Non-infectious

Abnormal Laboratory Finding

Grades 1-4 (n=463) %
Grades 3-4 (n=463) %
Decreased hemoglobin 83 26
Increased glucose 66 5
Decreased platelets 60 28
Decreased lymphocytes 57 18
Decreased leukocytes 53 9
Decreased magnesium 46 1
Increased alkaline phosphatase 40 4
Increased gamma glutamyl transferase 40 8
Increased creatinine 36 0.4
Decreased sodium 34 6
Decreased neutrophils 34 15
Increased aspartate aminotransferase 29 2
Decreased albumin 27 2

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

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GR-1853-0032

6 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women [see Clinical Pharmacology (12.1) of full prescribing information]. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow, see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

ZEJULA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with ZEJULA.

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months following the last dose.

Infertility

Males: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) of full prescribing information].

8.4 Pediatric Use

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

8.5 Geriatric Use

In PRMA, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. In NOVA, 35% of patients were aged 65 years or older and 9% were aged 75 years or older. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mild (Clcr: 60 to 89 mL/min) to moderate (Clcr: 30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily (see Dosage and Administration (2.4) of full prescribing information). Niraparib exposure increased in patients with moderate hepatic impairment (total bilirubin <1.5 x ULN and any AST level or bilirubin <1.0 x ULN and any AST level) and no dose adjustment is needed.

The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST level) [see Clinical Pharmacology (13.2) of full prescribing information].

17 PATIENT COUNSELING INFORMATION

Advise patients that ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including rash) in individuals with a history of aspirin hypersensitivity.

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose (see Use in Specific Populations (8.3)).

Lactation

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after receiving the last dose (see Use in Specific Populations (8.3)).

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after the last dose [see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)].

10 PRECAUTIONS

Continued
The ALK inhibitors are superior to chemotherapy both in the first-line setting and second-line setting. Brigatinib and lorlatinib are taken once daily, whereas alectinib is taken twice daily. They’ve all been compared head-to-head with crizotinib. All these treatments had higher response rates and substantially better PFS, and most importantly, incredibly high response rates in the CNS, which was much higher than what we see with crizotinib.

The ALEX trial [NCT02075840] was a head-to-head comparison of alectinib with crizotinib. The PFS favored alectinib (HR, 0.43; 95% CI, 0.32-0.58). The CNS PFS in those patients with and without brain metastases were evaluated, and there was much better PFS at 1 year, 2 years, 3 years, and 4 years compared with crizotinib. In fact, crizotinib failed to maintain progression-free time in almost all patients who had brain metastases past 1 year. The overall survival [OS] showed the superiority of [long-term] alectinib [65% with alectinib vs 45.5% with crizotinib (HR, 0.67; 95% CI, 0.46-0.98; P = .038)]. Interestingly, the active smokers crossed 1.00, but it was only a sample size of 17. Otherwise, pretty much everything else favored alectinib.

**Are there other trials of note for this treatment?**

The ALTA-1L trial [NCT02737501] studied brigatinib vs crizotinib. It’s important to know that crossover was allowed and that’s going to obscure OS, but it’s also important to know because of the [potential for] pneumonitis. Brigatinib should never be started at 180 mg/day, but it should be started at 90 mg/day for a week before it’s escalated to 180 mg. The incidence of pneumonitis goes down substantially when you do it in that dose-escalation fashion.

The investigator and independently reviewed PFS both favored brigatinib over crizotinib, as did the subgroup analyses. The brain metastases PFS [had a] much better control of not developing brain metastases at all, or controlling them, if you have brain metastases at baseline. The ORR was 74%, with a range of 66% to 81%, for brigatinib [OR, 1.73; 95% CI, 1.04-2.88; P = .034]. Two-year probability of maintaining the response was 50%, and about half the patients maintained their response there, even at the 4-year mark there was almost a flattening of the curve at around 2 years. The intracranial control, again, favored brigatinib. Remember there was crossover allowed, so you lose the OS advantage when patients are allowed to crossover and get brigatinib after they have already been on crizotinib.

The CROWN trial [NCT03052608] studied lorlatinib against crizotinib. No crossover was allowed, so when you look at survival, remember that. There was an impressive difference in PFS, with the largest difference compared with any of the other trials. Hazard ratio was 0.28, so the magnitude was greatest, and the PFS was favored in the lorlatinib arm in pretty much every subgroup [95% CI, 0.19-0.41; P < .001]. There were very high response rates in the group of patients receiving lorlatinib. The ORR was 76% [OR, 2.25; 95% CI, 1.35-3.89]. The median duration of response was not reached. Only 7% had progression as their best response.

The response rate in patients with brain metastases at baseline showed lorlatinib had a much higher CNS response and duration of response compared with those receiving crizotinib, 66% confirmed response vs 20% [OR, 8.41; 95% CI, 2.59-27.23], but that’s if you combine measurable and nonmeasurable. Now if you just look at measurable brain metastases, there were 82% confirmed responses and 71% complete responses. With the OS, no crossover was allowed, so you do see the separation of the curves, nonstatistically significant at [the time of publication (HR, 0.72; 95% CI, 0.41-1.25)].

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

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I typically extrapolate from the data we know with **EGFR** and **ALK**, where we have huge robust data sets, and those studies show that you should consider doing gamma knife or stereotactic radiation to the brain metastases.”

—NASSER H. HANNA, MD
Targeted Oncology™: Can you discuss using risk assessment tools in scoring myeloproliferative neoplasms (MPNs)?

MESA: What I tell our fellows is that there’s a prognostic score for every disease [and sometimes] more than one. Clinicians are busy; you’re trying to keep track of many different diseases. It’s impractical to memorize all these things. I think knowing where to find the scores is helpful, but more importantly, in what situation is it the most helpful? From my end, I always think that it’s interesting to look at what ends up being predictive and what that tells us about the biology of the disease. Because I see a lot of patients with MPNs, but I might also see CML [chronic myeloid leukemia], MDS [myelodysplastic syndrome], AML [acute myeloid leukemia]; and to some degree, a lot of the prognostic features overlap in these diseases. They’re cousins of one another. With worsening cytopenias, moving more toward AML and higher-risk molecular features, it’s only natural that patients have a worse prognostic score.

What about prognostic scoring in myelofibrosis [MF]? For MF you have the IPSS [International Prognostic Scoring System] and the DIPSS [dynamic IPSS].1-3 The IPSS is at diagnosis; the DIPSS can be used at any time. Practically around the world, the DIPSS and the DIPSS-Plus are used by far the most commonly.3,4 Because with peripheral blood counts and asking [about] symptoms and age you have a rough idea regarding survival, and that can be helpful for separating out the high-risk patients, or likely, the low-risk patients. The additional molecular mutations are relevant. It doesn’t take away those clinical features, but it’s clearly relevant. These other variables are as follows: 1, if there’s significant fibrosis, and 2, the absence of CALR type 1.5,6 It’s a little awkward way of saying it, but basically being CALR type 1 mutated is more favorable; if they have CALR type 2, they do worse. If you have JAK2 or MPL or if you are lacking any of those driver mutations, you are triple negative. Or if you have a higher-risk molecular feature: ASXL1 is a bad actor, and it’s a bad actor also in MDS; again, it’s telling us something about the biology of the disease. [Additionally, if you have] EZH2, IDH1/2, or SRSF2, or if you have more than 1 of these, [it is a high-risk feature].

The MIPSS70 [mutation-enhanced IPSS 70] can help to separate those patients who have a pretty long survival from the other side, [patients who] might have a very poor survival.5,6 If I’m on the fence about someone—they’re aged 58, they have some mild anemia—this is exactly the sort of patient I’m going to do that extended panel on to try to get a sense of whether we should be thinking about stem cell transplantation. If an individual is aged 79, it’s probably not going to make a big impact one way or the other. There is a second model [MIPSS70-Plus version 2.0].6,7 This is, to some degree, splitting hairs. I think it’s the transplanter who drilled down a
bit more into this, to refine that prognosis to the best degree that you can, as they’re trying to factor in who the donor is and what the comorbidities are for the patients. Really, [they are] trying to weigh the risk and benefit of transplant vs no transplant.

Now, the MF secondary to polycythemia vera [PV] and essential thrombocythemia [ET] prognostic model—again, it may seem too much in terms of too many scores—this one is a bit complementary. Patients who had evolved from PV or ET are similar, but not exactly the same, as [those with] primary MF. The biggest functional difference is that the blood counts tend to be more preserved in these patients. So, if they had PV before, they tend to become anemic at a lower rate, because there’s still more residual erythrocytosis left in the bone marrow. I’ve had patients who have died of AML, from post-PV MF, who still never became anemic, or still had a hemoglobin of 12 g/dL. It can confound that value.

Likewise, if they have ET, becoming thrombocytopenic sometimes doesn’t occur. There are individuals who have died of MF, with post ET MF, who still had a platelet count of 200,000/µL. Again, they’re not always predictive. So this is helpful, but it’s primarily a refinement for the stem cell planter. For physicians, knowing more than the DIPSS the MIPSS probably doesn’t help your practice to a significant degree.

**Is the CALR mutation protective against clots, protective against transformation, or both?**

In ET, it is less associated with thrombosis. Now, is it the CALR mutation itself that’s more protective, or is the biology a little different? I don’t think that we know. In MF, it has a longer survival, but it’s not necessarily associated with the issue of thrombosis. So it is helpful for both of those conditions but for slightly different reasons. We may end up finding, in the end, that CALR-mutated disease is similar but is different enough that it should be considered separate. For the time being, we still largely treat them the same but factor in a prognostic score.

**What about the National Comprehensive Cancer Network (NCCN) guidelines for MF?**

For the NCCN guidelines, I was the initial panel chair. It’s now fallen to my colleague Aaron Gerds, MD, MS. But they decided, and I think wisely so, that with all these scores, functionally, it probably doesn’t have implications for therapy beyond stratifying patients into lower risk or higher risk groups. In higher risk, which fits this patient, we assess symptoms but we stratify the treatment in part on platelets. So first we determine, are they a transplant candidate or not a transplant candidate? If they’re a transplant candidate, we certainly consider moving toward a transplant.

Now usually [this is] in concert with starting them on medical therapy. Initially, we have questions such as is it safe to use a JAK inhibitor before transplant? Largely, we have found that is the case. We also have found that the outcome with transplant is probably best if they have the transplant while they’re optimally responding to a JAK inhibitor. If we wait until they’re on a JAK inhibitor and progress, if they’ve failed it, particularly if they’ve moved to acute leukemia, the outcomes are worse. I try to share with my patients, “The optimal time for transplant is probably a bit before you feel that you need one.” Because if we’re using it as a salvage therapy, the outcomes are probably a bit poorer.

All of that said, probably less than 10% of patients with MF in the United States [receive] a transplant. That’s due to age, choice, a range of factors. The majority in the United States receive ruxolitinib (Jakafi). Fedratinib (Inrebic) is now approved in the frontline setting. Not many have used it in that setting, but it is approved and there are circumstances when to consider it. It probably is more commonly used in the second-line setting, and that is approved as well.

**Can you give more detail about ruxolitinib?**

Now ruxolitinib, it’s almost a decade that it has been around, [as seen in the] New England Journal of Medicine studies that were published long ago: ruxolitinib vs placebo, or ruxolitinib vs best alternative therapy. It was shown to be very helpful for improvement in the spleen and the control of symptoms.

We have used it over this period of time. Sometimes, the effect can be quite dramatic. I’d say because of the availability of this we tend to see [fewer] patients now with these extreme presentations, because they usually have already been treated. But there was—I think pre-2007, pre-JAK inhibitor—a time when we had patients with gargantuan spleens and cachectic patients. That still occurs, but fortunately that occurs in fewer patients.

There clearly can be improvement in symptoms. Patients with MF can be quite symptomatic....Symptoms include fatigue, night sweats, weight loss. There can be some symptoms related to the spleen, some that are hypercatabolic and some that are associated with progressive disease.

With other patient-reported outcome metrics, ruxolitinib showed improvement in quality of life, as well as global health status.

Now over time, I think we have been able to answer the question, “Is there an impact on survival?” The studies were not survival studies because of many reasons, starting with the impractical nature of keeping [participants] on a control arm indefinitely with a drug that made a difference. But there are now many real-world analysis data, as well as long-term follow-up from
What we have learned over time is that—and it’s probably not a surprise—survival is really associated with the quality of [the patient's] response and the degree of improvement in the spleen correlates with survival. I don’t think that it’s a mechanical thing, meaning that it’s because the spleen shrank that they lived longer.”

—RUBEN MESA, MD

the trials accounting for crossover, as well as other pieces, suggesting that there is an improvement in survival.\(^{13}\) It’s not a cure; the survival curves do not plateau.

**Why do you think patients live longer when receiving ruxolitinib?**

I think it’s a range of things. There may be less inflammation in the bone marrow, less drive toward progression, toward acute leukemia.\(^2,13\) I think there is less debilitation. All of these things play a factor. But in caring for hundreds to thousands of patients with MF, without question [I’ve seen that] these patients are living longer. I have some patients who are still alive from 2007 who [previously might have died] in 2 to 3 years, so there are some extremely long-lived patients. The average is less; I think the impact is real, but it is finite.

What we have learned over time is that—and it’s probably not a surprise—survival is associated with the quality of their response and the degree of improvement in the spleen correlates with survival.\(^{14-16}\) I don’t think that it’s a mechanical thing, meaning that it’s because the spleen shrank that they lived longer. I think whatever is associated with JAK inhibitor–treated patients living longer corresponds to the improvement in the size of the spleen.

Is that cytokine driven? Is that improvement in the inflammatory microenvironment in the bone marrow? Whatever that is, I think there’s a correlation but I don’t think that it’s just about the spleen.

**How is ruxolitinib dosed for patients? What is the safety profile?**

One thing we have learned over time is that we probably have grown a bit too conservative in terms of the dosing. Doses below 10 mg twice daily probably don’t have a significant impact on the splenomegaly, and probably don’t have a huge impact on survival. There is probably some value to trying to get patients to 15 mg twice daily or, in certain circumstances, even 20 mg twice daily.\(^{17}\) If they’re anemic, I tend to be patient. If they need a transfusion or 2, I warn them that that is a possibility up front.

I think over time we’ve done a variety of analyses, and it probably is worthwhile to hold the dose steady and support them during that time. In terms of toxicities, in JAK inhibition—the creation of red cells and platelets both go through the JAK/STAT pathway. So it was predictable from the beginning, that lowering red cells and platelets would be, not even a toxicity, just a predicted effect based on the mechanism of action. The DLT [dose-limiting toxicity] was clearly platelet-related.\(^{11,12}\) Neutropenia is quite uncommon.

There have been studies looking at, for patients with lower platelets, what is the best approach.\(^{18,19}\) There are increasing data suggesting it’s OK to start them low but push the dose. If a patient has 60,000 platelets, it’s OK to start them on 5 mg twice a day. But they’re not stuck at that dose.

The likelihood of, once they’re on a JAK inhibitor, having a big drop in their platelets as a secondary effect is probably less. So they were able to take [patients] who started with platelets of 50,000 to 74,000, or 75,000 to 100,000, and get them to 15 mg twice a day. Not at first, but they walked the dose up, and that probably is a bit more effective dosing for these patients.

Now with these patients, they started with thrombocytopenia. Interestingly, for the patients with platelets of 50,000 to 74,000, further decreases from baseline really weren’t very high.\(^{19}\) It’s been my experience that the lower the platelet count, probably the less the delta. I have started patients on 5 mg twice a day who have a platelet count of 40,000, but it’s not like they dropped to 5000. They’ll drop to 32,000. Whereas, if you start somebody at 300,000, yes, they may drop to 150,000. What we
don't tend to see is JAK inhibitors causing platelet counts of under 10,000 or having patients hemorrhage. So there can be thrombocytopenia, but it’s a little different from a straight myelosuppressive effect.

What are the data for fedratinib in this setting?
Fedratinib...is a JAK2 and FLT3 inhibitor. It was approved in September 2019, so a little bit before the COVID-19 pandemic started.10 [The approval was] based on the randomized phase 3 JAKARTA study [NCT01437787], which was fedratinib vs placebo. It very much was a contemporary of ruxolitinib.20,21 It was not compared against ruxolitinib because it was tested somewhat in parallel, perhaps just a little bit further behind, but this study started before ruxolitinib was approved.

Very much like ruxolitinib, there was good improvement in splenomegaly and symptoms.20,22 There was efficacy both for individuals with a platelet count above 100,000, as well as from 50,000 to 100,000. In terms of toxicity, the potential for cytopenias is relatively similar to that of ruxolitinib.21 It can cause gastrointestinal adverse events. Having used it in a range of patients [throughout Texas], I tend to start prophylactic medication; many patients are able to come off of these. The medicine has a black box warning for Wernicke encephalopathy, which is very rare—in the clinical trials, which had led to a hold—less than a 1% rate. It may interfere a bit with thiamine metabolism. Subsequent to that hold, now, with the black box warning, we screen for thiamine and we replace thiamine.

Thiamine is easy to give, it’s [inexpensive]; I pretty much put all my patients on it who go on the medicine; they are screened for this. We’ve not seen that it’s been an issue after its approval, with monitoring for thiamine. So it’s something to be aware of, but functionally not a big deal.

A jug of 100 thiamine [tablets], when I went down to the pharmacy, was less than 10 dollars. About Wernicke encephalopathy: There is less than a 1% absolute risk, and [it is] something that shouldn’t be viewed as an excessive barrier.23 Give them some thiamine, measure the level, track it, but it’s not too big a factor.

What do you think about using fedratinib for patients with MPNs?
Fedratinib is a good drug....It’s a drug a lot of people aren’t super familiar with. In part, with COVID-19 and everything else, we’ve not been at the American Society of Hematology annual meeting and...have heard about it less. There was a delay between its phase 3 studies and its approval. So a lot of the things that usually build momentum in terms of usage weren’t there.

We can see some nice responses in the second-line setting. I think for most who are pretty comfortable with ruxolitinib, the second-line setting is the most natural. I’d say I had [approximately] 10 to 15 patients during COVID-19 [for whom] I would have normally considered a clinical trial, [but] putting them on a clinical trial was impractical. They didn’t want to come down from Dallas or somewhere else if they needed a second-line therapy. So we used fedratinib and got some good responses. Patients can tolerate it. It’s a good thing to consider in the second-line setting, particularly if traveling for a clinical trial is not attractive.

Just going back to the NCCN treatment algorithm, no response or loss of response to that initial JAK inhibitor therapy is where an alternative JAK inhibitor may be considered. [And that], at this point, is fedratinib.7 [For patients with] platelets of less than 50,000, “not a transplant candidate” equals “consider clinical trial.” It is possible that soon we may see a third JAK inhibitor, pacritinib, approved. That has been tested in individuals with a platelet count less than 50,000 and was helpful. So there may be a new option for those individuals in the frontline or second-line setting who have marked thrombocytopenia.

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

Best Practices to Monitor Recurrence in Patients With Follicular Lymphoma

Kami Maddocks, MD, discusses what findings and signs clinicians should look out for when monitoring disease recurrence in patients with follicular lymphoma.

View more at: TargetedOnc.com/link/1756
INDICATIONS
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
• Metastatic castration-sensitive prostate cancer (mCSPC)
• Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA® and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA® and in 7% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3.9% of patients treated with ERLEADA® and 1.5% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 3% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® (see Use in Specific Populations (8.1, 8.3)).

ADVERSE REACTIONS
The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
• Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)
• Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.9%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0.0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1.3%); 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.

The following TITAN primary analysis results are included in the ERLEADA® Prescribing Information:
Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053.
therapy to achieve a 35% reduction in the risk of death in FDA-approved labeling for mCSPC (ERLEADA® and ADT vs placebo + ADT; median OS: NR vs 52.0 months; HR = 0.65; 95% CI: 0.53, 0.79).6,12

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 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, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP3A4 or CYP2C19 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, the ERLEADA® dose should be based on tolerability (see Dosage and Administration [2.2]).

Effect of ERLEADA® on Other Drugs: CYP3A4, CYP2C9, CYP2C19, and UGT Substrates — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C9, or CYP2C19 may result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is concomitant. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyltransferase (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 — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

ADT = androgen deprivation therapy; AR = androgen receptor; CI = confidence interval; CT = computed tomography; GnRH = gonadotropin-releasing hormone; HR = hazard ratio, mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; NE = non-estimable; nmCRPC = non-metastatic castration-resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen; pFS = radiographic progression-free survival; SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-509; TITAN = Targeted Investigational Treatment Analysis of Novel Androgen.


Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.
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, weight decreased, hypothyroidism, hypertension, flushing, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardiac-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 ≥5% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

### Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ADVERSE REACTION</th>
<th>ERLEADA N=524</th>
<th>Placebo N=520</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
<td>All Grades %</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia a</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash b</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=520</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
<td>All Grades %</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertiglyceridemia a</td>
<td>17</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 26 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 hematia. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (≥2%) were fracture (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, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>Placebo</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>1.4</td>
<td>28</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>25</td>
<td>5.2</td>
<td>6</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>42</td>
<td>0.1</td>
<td>9</td>
<td>0</td>
<td></td>
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<tr>
<td>Peripheral edema</td>
<td>21</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fall</td>
<td>42</td>
<td>1.7</td>
<td>9</td>
<td>0.8</td>
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<tr>
<td>Fracture</td>
<td>12</td>
<td>2.7</td>
<td>7</td>
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<tr>
<td>Investigations</td>
<td>42</td>
<td>1.1</td>
<td>6</td>
<td>0.3</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>14</td>
<td>20</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>14</td>
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<td>9</td>
<td>0</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>1.1</td>
<td>15</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>0</td>
<td>16</td>
<td>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 genitai, 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).

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>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
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<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
<td>64</td>
<td>0.5</td>
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<tr>
<td>Leukopenia</td>
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<td>0.3</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>1.8</td>
<td>21</td>
<td>1.6</td>
</tr>
<tr>
<td>Chemistry</td>
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</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76</td>
<td>0.1</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>70</td>
<td>2</td>
<td>59</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>67</td>
<td>1.6</td>
<td>49</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>32</td>
<td>1.9</td>
<td>22</td>
<td>0.5</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.

**Respiratory, Thoracic and Mediastinal Disorders:** interstitial lung disease

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

**DRUG INTERACTIONS**

**Effect of Other Drugs on ERLEADA**

**Strong CYP2C8 or CYP3A4 Inhibitors**

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase exposure 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.

**Effect of ERLEADA on Other Drugs**

**CYP3A4, CYP2C9, CYP2C19, and UGT Substrates**

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

P-gp, BCRP or OATP1B1 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1) in Full Prescribing Information]. There are no available data on ERLEADA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥2 times the human clinical exposure (AUC) at the recommended dose [see Data].

Data

Animal Data

In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance, misspaped pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar ribs), and small, incomplete ossification, and/or misspaped 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 8 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.

PATIENT COUNSELING INFORMATION

Advise 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].
RENASAL CELL CARCINOMA

Roundtable Discussion: Tykodi Looks at Multiple Regimens for Managing Renal Cell Carcinoma

CASE SUMMARY

A 59-year-old Black woman received a diagnosis of clear cell renal cell carcinoma (RCC) and underwent a left tonal nephrectomy in December 2019. Nine months later, she developed metastatic disease to bilateral lung, mediastinum (35 × 38 mm), and retroperitoneal lymph nodes. She then received a diagnosis of stage IV RCC with clear-cell histology and metastases to the lung and retroperitoneum. Her Karnofsky performance status score was 90%. Her hemoglobin, neutrophils, and platelets were within normal limits. Her elevated corrected calcium was greater than the upper limit of normal.

DISCUSSION QUESTIONS

- How do you assess patient risk?
- Does risk status influence your frontline decision-making for a patient such as this?
- What additional workup do you typically order?
- Would you initiate systemic therapy at this point?

AHED: I like to do positron emission tomography [PET] scans; some of them will light up like Christmas trees and then some others don't light up at all. It’s good to know [that information] from the get-go.

TYKODI: Do you find that you [have] trouble with insurance providers declining PET scans for kidney cancers?

FAHED: It depends on which plan [the patient has]. I have, in general, a lot of denials, and I have to go and appeal. That’s kind of routine.

TYKODI: What about the findings? Obviously, if you had bony lesions that you hadn’t seen on body imaging, that would probably influence at least applying bone-directed therapy.

But is there anything about the PET imaging, the intensity uptake or finding a couple of spots you didn’t see on CT imaging, that might influence...your choice of therapy?

FAHED: For this patient, this is a first recurrence, and what we saw on CT imaging were some deposits in the left upper quadrant, so it wasn’t a clear-cut recurrence. Unfortunately, it did not help much in this situation.

TYKODI: For most patients with kidney cancer, would you try to get a baseline PET scan? Is that how you like to manage [this situation]?

FAHED: I see that it helps with my [patients with] bone metastases. The CT scan is not the best test to see bone metastases. A PET scan, a lot of times, does not show any bone lesions, but then you do a PET scan and you see plenty of metastatic disease.
I think that risk factors most commonly divide the population between local RCC that relapses later and synchronous metastatic disease, where you start treating [right at the time of diagnosis]. That’s the typical distinction. There’s always the odd patient that you follow, maybe [one who has] small lung nodules for a while, and they [survive beyond] a year.”

—SCOTT TYKODI, MD, PHD

**CHINTAPATLA:** For me, this patient has hypercalcemia, [so I would] initiate a bone scan. Typically, I don’t do CT scans in the kidney setting.

**ZHANG:** I don’t typically do a PET scan, either. On some occasions, if we want to confirm oligometastatic disease, I may do it, but I generally would do a brain MRI. I do get a brain MRI for every patient. I think...that will be in line with European recommendations to get a brain MRI.¹

**TYKODI:** You’re saying you do it on everyone? It’s not guided by your sense of the patient’s risk...or negative histological results?

**ZHANG:** I think...that high-risk patients—for example, a patient with lung metastases and mediastinal lymphadenopathies—those are more likely to have brain metastases and there are some retrospective data on that, but occasionally we see surprises. Even for the patient with very good systemic control, they may have brain recurrence. I got burned a couple of times, so I started to do it more often.

**TYKODI:** I think the intent [in this case] was that [the patient] has new metastatic findings at 9 months from their nephrectomy, so you’re at less than a year and you’re falling within that time interval that would be a risk factor. But yes, you’re right, that is a little bit confusing.

I think that risk factors most commonly divide the population between local RCC that relapses later and synchronous metastatic disease, where you start treating [right at the time of diagnosis]. That’s the typical distinction. There’s always the odd patient that you follow, maybe [one who has] small lung nodules for a while, and they [survive beyond] a year.

Any other comments on work-up? Does anybody feel strongly about gene panel testing? Do you incorporate that into your practice, and if you do, what sorts of findings are [affecting] your choice of therapy?

**FAHED:** Before I didn’t, but I’m starting to think about it.

**TYKODI:** I think The Cancer Genome Atlas [states] VHL mutations are the most common or some of the most common, but you can have chromosome deletions where you lose an allele as well, that wouldn’t show up on your [next-generation sequencing] panel.

But then the question is: How does that influence your therapy, if you know they [have] a clear cell histology? Are there certain genes? Are you looking for mTOR pathway genes, or is there anything about the panel that would sway you in terms of how you choose your initial therapy?

**FAHED:** No, no preferential therapy for me.

**POLLING QUESTION**

“A decision was made to initiate systemic therapy. What frontline therapy are you most likely to choose for this patient?”

- Axitinib/pembrolizumab 40% (4)
- Cabozantinib/nivolumab 20% (2)
- Nivolumab/ipilimumab 20% (2)
- Lenvatinib/pembrolizumab 10% (1)
- Other 10% (1)
- Cabozantinib 0% (0)

**TOTAL VOTES: 10**

**TYKODI:** [When I look at the data from the CLEAR trial (NCT02811861)], what stands out to me is the high bar in the efficacy data, the high response rate, the provocative progression-free survival [PFS], and the high complete response [CR] rate.² How are you going
to integrate pembrolizumab [Keytruda] and lenvatinib [Lenvima] into your practice, and are the data for efficacy a game-changer [to you all]?

**CHINTAPATLA:** I think in terms of the adverse effects [AEs] with lenvatinib [I would] not use that in treating patients with kidney cancer at this time.

**TYKODI:** How do you manage [the treatment] and adjust your practice [after] considering the CLEAR data?

**QURESHI:** I want to see some maturity of the data, but I [voted for] ipilimumab [Yervoy] and nivolumab [Opdivo], but I like pembrolizumab and axitinib [Inlyta] as well, especially if there are any brain metastases.

**CHAVES:** I think it’s a good option for first-line treatment. I’ve been more on board with axitinib and pembrolizumab previously, and I’ll have to look at the AE data [to compare] it with that, but I think it’s a good option.

**CUI:** I haven’t used this combination, but I use them individually for other cancers. The hypertension [that can result from taking] lenvatinib, probably to me, is more pronounced than diarrhea. I don’t know if the combination of those 2 drugs makes diarrhea worse, but the efficacy seems to be appealing.

**ZHANG:** I think the response rate and the CR rate are very impressive, but you know that those are used in this regimen. Lenvatinib, [when the dose is] 20 mg a day is high, and I’m concerned about the tolerability. I would consider a patient with a very high tumor burden, if I need a faster response.

**TYKODI:** What about lenvatinib in general? Have you used it with everolimus [Afinitor] in the salvage setting, and do you find it any more or less challenging to work with than any of the other TKIs [tyrosine kinase inhibitors] that you commonly use?

**WALLEN:** I haven’t used it for [patients with] RCC. I’ve used it for hepatomas on a rare occasion, but I agree with the others, that the tolerability is probably my biggest concern. The nice feature with axitinib is it’s very titratable and you can dial it up or down fairly easily.

**WONG:** I had a patient on lenvatinib and everolimus, and he was in kind of poor shape, but he couldn’t tolerate the lenvatinib, so we had to just take it off eventually and keep him on everolimus.

**CUI:** [For one patient I had,] the combination was hard. Both of those were reduced because of hypertension, even fluid overload. It’s a pretty harsh regimen.

### CASE UPDATE

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

**TYKODI:** To remind you all, the lenvatinib and pembrolizumab regimen starts with lenvatinib at 20 mg in combination with pembrolizumab. The everolimus and lenvatinib combination that’s currently approved as salvage therapy starts lenvatinib at 18 mg. You’re starting higher than the current use in the everolimus regimen.

So are you inclined to just dive in at 20 mg? Are you inclined to dose reduce, and what are you doing with lenvatinib and everolimus? Do you always start patients at 18 mg? Do you find that to be challenging?

**ZHANG:** I think I would start with 18 mg because if a patient cannot tolerate it then you may lose a patient. They lose interest in continuing. I think I would start at 18 mg instead of 20 mg, and you can always go up if they do well.

**TYKODI:** In the CLEAR study—and in many of the front-line studies—the immunotherapy [IO] duration is capped at 2 years, but the TKI is allowed to continue. Have you had patients get to a full 2 years of therapy, and then what are you doing for those patients? Are you continuing a TKI? Are you continuing the IO/TKI and not being completely faithful to how the study was done? What are your thoughts about transitioning at 2 years?

**QURESHI:** It depends on the patient, but you know, I had a patient who still has autoimmune hepatitis as a result of her IO, so she went off. But she has remained disease-free for 2 and a half years now.

**WEINER:** I think if they’re doing fine and they’re not having any problems, I would be hesitant to stop things.

**WALLEN:** I think after 2 years, if they had a good response, I would probably start thinking about tapering the IO portion, not necessarily giving it every 3 weeks or every 4 weeks but giving it less frequently—maybe every 12 weeks or so—but continuing the TKI.

**TYKODI:** Has anyone had an insurance provider terminate the coverage at 2 years saying that that’s the maximum allowable duration?
INKLAB: Yes, that’s always the problem, and it depends on the diagnosis, but most of the time, for lung cancer, you will have to stop at 2 years if you have stable disease or no evidence of disease. However, if most of your patients are on Medicare, it’s not as much of an issue.

ZHAHNG: I think after 2 years, if they had a good response, I would probably start thinking about tapering the IO portion, not necessarily giving it every 3 weeks or every 4 weeks but giving it less frequently—maybe every 12 weeks or so—but continuing the TKI.

ANAND: I’ve used this regimen recently in a patient who had a very large tumor and metastatic disease, and she had an excellent response within 3 months and symptomatically, even after the first 2 treatments, she improved. I like this regimen, it’s very well tolerated, and her performance status improved significantly.

WALLEN: I like this regimen as well...for patients who have low tumor burden or relatively limited pulmonary metastases. I like ipilimumab and nivolumab in the first line because I think you don’t necessarily need to have a rapid response, but for [patients who] need a more rapid response, I like the IO/TKI.

This is probably 1 of my 2 favorites. The axitinib is great, too, just because it’s so eminently titratable. I think they’re comparable if you’re able to titrate the drugs up to maximum tolerable dosage.

WONG: Compared with the CLEAR trial, where [more than] 50% of patients stopped at least 1 of the drugs, in this trial it’s only 15%.

TYKODI: In CLEAR, yes, you have nearly 20% of patients stopping 1 of the 2 drugs. You should be able to add those together for stopping, because it’s the opposing drug, and then, another 10% dropping the entire regimen. Fifty percent of patients are either reducing therapy to a single drug or stopping entirely, and it’s quite different. It’s a third of that in CheckMate 9ER [NCT03141177].

I’m curious about the practitioners who are in smaller communities, [such as] Montana and Idaho and Wyoming. Do you feel that toxicity management in patients who might geographically be more dispersed than [those in an urban environment such as Seattle, is that more of a concern, more of an issue? Would you shy away from a regimen that you’re fearful is going to make [patients] quite ill? Do you think there’s a difference?

WEINER: I do shy away from it if a [patient] has a long travel time to get in, has difficulty coming in. I do shy away from it, but I probably go more by their performance status than anything.

QURESHI: Yes, my patient population lives close to the clinic, so I don’t have too much of an issue, but if someone’s coming from far away, I will think about that, but it doesn’t usually influence my treatment decision too much.

REFERENCES


DISCUSSION QUESTIONS

What are your reactions to the CheckMate 9ER data?
How will you counsel patients regarding this regimen?
What is your impression of the safety/tolerability of this regimen?
Are you familiar with the recommended dosages for this regimen?
How would you use of this combination in the frontline impact your second-line decision-making?

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

Deciding on Treatment for a Patient With CD10+, CD20+ DLBCL

CASE

A 75-year-old man presented with fever, a 7-lb unintentional weight loss, and occasional chest pain.

- Medical history: hypertension, medically controlled; poorly controlled type 2 diabetes
- Physical exam: appeared tired; palpable bilateral cervical lymphadenopathy
- Laboratory results:
  - Lactate dehydrogenase: 300 U/L
  - Hemoglobin: 10.8 g/dL
  - Bilirubin: 1.3 mg/dL
  - Creatinine: 1.7 mg/dL
  - All other values: within normal limits
  - HIV, hepatitis B and C: negative
- Lymph node biopsy:
  - Immunohistochemistry panel: CD10+ and CD20+ confirmed diffuse large B-cell lymphoma (DLBCL)
  - Fluorescence in situ hybridization: negative for rearrangements of BCL6, BCL2, and MYC
- Imaging studies:
  - Whole-body PET/CT scan showed activity in colonic walls—largest node, 3.9 cm; evidence of subcutaneous tissue involvement.
  - MRI of the brain showed no evidence of lesions.
- Staging: stage IV; International Prognostic Index score, high risk; Ann Arbor stage III/IV
- ECOG performance status: 1
- The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone), which he tolerated well.
- PET scan at the end of treatment showed complete remission (CR).
- One year later, the patient presented with diffuse lymphadenopathy, confirmed by PET/CT scan.
- Biopsy showed relapse of DLBCL.
- The patient declined transplant.

Targeted Oncology™: What are some options for the second and subsequent lines of therapy in this patient?

PAGEL: The NCCN [National Comprehensive Cancer Network] guidelines break down [therapy for DLBCL] into those for transplant candidates or nontransplant candidates. Our patient in this case is not a transplant candidate. For the second and subsequent lines of therapy, there are some interesting chemotherapy-based regimens that we have a long history with.1 Polatuzumab vedotin [Polivy] plus or minus rituximab and bendamustine [Treanda] is approved by the FDA for patients who have failed 2 or more prior lines of treatment.1 Polatuzumab is an antibody-drug conjugate that targets CD79b on the surface of the B lymphocytes, and delivers a payload, which is the MMAE [monomethyl auristatin E] chemotherapeutic agent, internally to the cell like a smart bomb.

Tafasitamab [Monjuvi], an anti-CD19 antibody plus lenalidomide is also approved by the FDA.2 I think it's been an exciting regimen, as well, but we understand that it's only approved for people who are not eligible for transplant for any reason.2 It's important to remember patient preference can be a reason not to be eligible for transplant. The patient in our case refused the transplant, so it made that part easy.

Other options include lenalidomide [Revlimid] plus rituximab, bendamustine plus rituximab, brentuximab [vedotin; Adcetris] for rare cases of CD30+ DLBCL, and ibrutinib [Imbruvica] for very rare cases of non–germinal center B-cell-like [non-GCB] DLBCL.1

After following up [with] these patients and reassessing for response or progression...the choices are around alternative second-line treatments. [These include] allogeneic...
transplants or novel therapies such as loncastuximab tesirine [Zynlonta], another antibody-drug conjugate, [and] selinexor [Xpovio], which is approved for people who have failed at least 2 lines of therapy or have progressed on CAR [chimeric antigen receptor] T-cell therapy, which is in fact very much another option too.

I think it’s important to recognize that we don’t know if targeting CD19 with tafasitamab or loncastuximab, which both of these agents target, has a negative impact on anti-CD19 CAR T-cell treatment. We’re waiting for more data. The early data suggest that maybe it’s not a problem but just something to keep in mind.

CASE (continued)

The patient received combination tafasitamab plus lenalidomide.

What is the mechanism of action for tafasitamab and lenalidomide?

I think [tafasitamab plus lenalidomide] is an interesting regimen. Lenalidomide is not a new drug to anyone and, frankly, you probably know tafasitamab indirectly because it’s an anti-CD19 antibody that just targets a different antigen than rituximab.

There are data that suggest that the combination of these 2 agents works better than if you were to use either of them alone. In other words, they have a synergistic effect. The antibody is, of course, going to work just like rituximab works. You have antibody-dependent cellular cytotoxicity, and phagocytosis. You can have direct apoptosis, as well.

If you understand the management of rituximab, you can understand the management of tafasitamab. One of the nice things about targeting CD19 simply is that it’s not CD20. We give a ton of anti-CD20 antibodies and eventually, it doesn’t work as well for one reason or another. So having a different target is very reasonable. Most know lenalidomide from using it in multiple myeloma. It certainly has immunomodulatory capabilities, such as direct cell death, and activation of those host effector cells that may work well with the antibody. The activity of these agents is potentiated when given together, which has been shown in preclinical models, in vivo and in vitro.

Which data was the approval of combined tafasitamab and lenalidomide based on?

[The combination] was approved based on [findings from] the phase 2 L-MIND trial [NCT02399085].

We’re looking forward to the confirmatory data, but it was a simple study that used relapsed or refractory patients who had failed 1 to 3 prior therapies. They were not eligible for a transplant. Patients who were refractory to primary therapy were not eligible for the study, but you can imagine that treating them with something different might be very appealing if they’re not going to go for a transplant.

Tafasitamab is an infusion done at 12 mg/kg. You give it weekly for the first 3 cycles. In the first cycle, there’s an additional loading dose on day 4. After cycle 3 up to indefinitely, you deliver the antibody every 2 weeks. It is combined with lenalidomide for 21 of 28 days at the approved dose of 25 mg daily. The objective response rate [ORR] was the primary end point in this trial. There are longer-term follow-up data of this study, as well, and the data are quite encouraging.

Many of these patients will require a dose reduction [of lenalidomide] from 25 mg, for reasons I don’t really understand well. Patients with lymphoma tend to not tolerate lenalidomide quite as well as those with multiple myeloma, it seems, so dose reductions happen in about half of patients. It’s not uncommon...to go down to 15 mg and, [although] rarer, down to 10 mg or 5 mg, but it is not particularly common to have to stop therapy due to toxicity.

In the L-MIND trial, the median age of the patients was 72 and the oldest patient was 76. This is an ideal regimen

—JOHN M. PAGEL, MD, PHD
for older patients. The median number of prior therapies was 2. About 20% are refractory to primary therapy, 44% refractory to their last therapy, [and] 11% failed a prior transplant. Most of these patients didn’t have a known cell of origin, and about [one-fourth] of them had non-GCB DLBCL.\(^5\)

**What was the efficacy in the L–MIND trial?**

The data after a follow-up of almost 3 years show the CR rate was outstanding. At 35 months, 32 of the 80 patients were in CR, so 40% of patients were having a CR. The ORR in this very difficult high-risk population who cannot get a transplant is also encouraging, at about 46%. Even more encouraging than that is the extended, outstanding median duration of response, with people at well over 43.9 months maintaining their remission and doing very well.\(^5,6\)

The median progression-free survival (PFS) is about [1 year]. I think that’s extremely encouraging, again, when they’re not transplant candidates. They’ll stay on that every-2-week antibody infusion for long periods of time. Some of these people are out 2 years or more, doing very well, with a relatively plateaued PFS curve. Maybe some of the people on the overall survival (OS) curve will do well for a long time. The regimen of course is unique but has an outstanding chance to get a CR that might be very durable.

Patients who get CRs do best. A partial remission is certainly better than not having any remission but is certainly very limited. The median duration of remission was about 44 months, very encouraging in many ways. But how we will use it in the algorithm is something I think we’re still trying to figure out.

Probably, and not surprisingly, [using this regimen] earlier is better than later. So if you only had 1 prior therapy, you have almost a 50% chance of having a CR. If you’ve had 2 or more therapies, it’s about a 1 out of 3 chance of having that kind of remission. Getting a CR is important. Those are the people that have the longest durations of remission. The patients with the longest durations of remissions are the ones that get treated earlier, after 1 prior therapy. Not surprisingly, the median PFS, the earlier [the regimen] was used, was about 2 years, which is outstanding in this patient population, and median OS in these patients is almost 4 years or so.

This is very encouraging for a non–chemotherapy-based regimen in patients who are not transplant candidates because they had comorbidities, or their age or performance status wasn’t adequate, or maybe they didn’t respond to their salvage chemotherapy.

**Which toxicities are associated with tafasitamab/lenalidomide therapy?**

You’re going to get some cytopenia due to the lenalidomide. They’re not at all due to the tafasitamab. You manage these just like in multiple myeloma and figure out if you need to go from 25 mg to 20 mg a day, or from 20 mg to 15 mg, because there is a 27% chance of having grade 3 neutropenia. The important point, in my opinion, is that the cytopenia is due to the lenalidomide. So if you’re going to dose reduce, or change anything, you change the lenalidomide. The tafasitamab is never dose reduced because it’s not causing these problems.\(^5\)

The nonhematologic adverse events (AEs) comprise a long list, but I think one of the things that’s impressive here is a very low rate of grade 3 or 4 AEs. We saw a little bit of diarrhea, about 30%, and things that go along with lenalidomide such as edema, and perhaps other gastrointestinal issues like constipation as well.

About half of these patients will have to go down to 20 mg. But if you’re at 20 mg, about three-fourths of patients will complete the entire 1 year of therapy with lenalidomide.\(^5\) So you’re going to do very well with it. Most of these people are going to do, hopefully, very well for a longer time.

Discontinuations to the regimen are about 12%. Most regimens in this patient population and setting have discontinuation rates of around 25% due to AEs.\(^5\) So it’s a well-tolerated regimen. The infusion reactions were about 6% to 7%, [which is] not high. If it happens early, it’s managed just like a rituximab reaction.

Tafasitamab plus lenalidomide is given for 1 year with lenalidomide, and then you stop the lenalidomide and continue the tafasitamab every 2 weeks indefinitely. There’s a big difference [between the AEs in the first year of therapy and those on the tafasitamab monotherapy thereafter]. To reiterate, the AEs outside of the infusion reactions are due to the lenalidomide.\(^5\)

**How does tafasitamab plus lenalidomide vs lenalidomide alone compare?**

The RE-MIND study [NCT04150328] evaluated the combination of the tafasitamab and lenalidomide vs lenalidomide monotherapy. A large [cohort of patients got lenalidomide monotherapy] and 81 patients got tafasitamab plus lenalidomide, but there was no tafasitamab alone cohort. I wish there was and in a perfect world we’d have that, but we don’t. The CR rate in the cohort that [received] tafasitamab plus lenalidomide was about 40%, and it was only about 13% if they received lenalidomide alone.\(^7\) We use the [rituximab plus lenalidomide] regimen a lot in indolent lymphomas and this is our equivalent of adding an antibody to lenalidomide in DLBCL. It is a non–chemotherapy-based regimen that clearly has a better ORR, better CRs, and probably even a better OS rate when you look at the combination of tafasitamab and lenalidomide, given its synergistic effects, for people that are not transplant candidates.
For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

A WAY IN WITH TRODELVY

TRODELVY attacks mTNBC with an antibody-drug conjugate (ADC) that binds to Trop-2.1

Based on preclinical data. May not correlate with clinical outcomes.

INDICATION
TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: NEUTROPENIA AND DIARRHEA

• Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.
• Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.

CONTRAINDICATIONS

• Severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

Diarrhea: Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.3% of patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Pre-infusion medication is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

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CONTRAINDICATIONS

IMPORTANT SAFETY INFORMATION

For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

PROVEN SURVIVAL BENEFIT

Nausea and Vomiting: Nausea occurred in 66% of all patients treated with TRODELVY and Grade 3 nausea occurred in 4% of these patients. Vomiting occurred in 39% of patients and Grade 3-4 vomiting occurred in 3% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV). withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to Grade ≤1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate–glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of Grade 3-4 neutropenia was 67% in patients homozygous for the UGT1A1*28 allele and 46% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 function.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

ADVERSE REACTIONS

In the ASCENT study (IMMU-132-05), the most common adverse reactions (incidence >25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence >25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.


Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.
NAUSEA occurred in 4% of patients. VOMITING occurred in 39% of patients. Grade 3-4 vomiting occurred in 3% of these patients. Grade 4 infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Permanently discontinue TRODELVY for life-threatening infusion-related reactions. Premedication: Prior to each dose of TRODELVY, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended. Premedicate with antipyretics, H1 and H2 blockers prior to each dose of TRODELVY for patients with prior chemotherapy reactions. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK receptor antagonist, as well as other drugs as indicated).

The Modifications of Neutropenia: Stop or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions. Dose Adjustments for Adverse Reactions: Withhold or discontinue TRODELVY to manage adverse reactions as described below. Do not re-evaluate the TRODELVY dose after a dose reduction for adverse reactions has been made. Severe Neutropenia, defined as Grade 4 neutropenia (ANC < 1000/mm³) or Grade 3-4 febrile neutropenia (absolute neutrophil count or ANC < 1000/mm³ and fever ≥ 105.8°F), OR at time of scheduled treatment, Grade 3-4 neutropenia which delays by 2 or 3 weeks for recovery to ≤ Grade 1.

At first occurrence, 25% dose reduction. At second occurrence, administer granulocyte-colony stimulating factor (G-CSF). At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY. At time of scheduled treatment, Grade 3-4 neutropenia occurs which delays beyond 3 weeks for recovery to ≤ Grade 1, discontinue TRODELVY at first occurrence.

Severe Non-Neutropenic Toxicity: defined as Grade 4 non-hematologic toxicity of any duration. OR any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents. OR other Grade 3-4 non-hematologic toxicity persisting >48 hours despite optimal medical management. OR at time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays by dose 2 or 3 weeks for recovery to ≤ Grade 1.

At first occurrence, 25% dose reduction. At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY. In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks, discontinue TRODELVY at first occurrence.

CONTRAINDICATIONS

Also see Warnings and Precautions

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

Warnings and Precautions

Also see BOXED WARNING, Dosage and Administration, Contraindications, Clinical Pharmacology, Nonclinical Toxicology, and use in Specfic Populations

Neutropenia: Severe (Grade 3-4) neutropenia can occur in patients treated with TRODELVY. Neutropenia occurred in 61% of patients treated with TRODELVY, Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7% of patients. Withhold TRODELVY for ANC below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 1 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Diabetes: TRODELVY can cause severe diabetes. Diabetic symptoms occurred in 65% of all patients treated with TRODELVY. Diabetes occurred in 12% of all patients treated with TRODELVY. One patient had pre-existing diabetes and was started on TRODELVY. One patient had pre-existing diabetes and was started on TRODELVY. One patient with prior diabetes who had poor glycemic control was placed on a diet and exercise program. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholestatic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive uridine diphosphate-glucuronosyl transferase (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of neutropenia and anaemia was analyzed in 701 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 3-4 neutropenia was 28% for patients homozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=313). The incidence of Grade 3-4 anaemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 1% in patients with the wild-type allele. Patients with the UGT1A1*28 allele were at increased risk for adverse reactions. Withhold or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embry-ey fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, 36-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for at least 3 months after treatment.

ADVERSE REACTIONS

Also see BOXED WARNING, Warnings and Precautions, and Clinical Studies

The pooled safety database described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in 705 patients from three studies, IMMU-132-01, IMMU-132-05 and IMMU-132-12 which included 366 patients with mTNBC who had received prior systemic chemotherapy for advanced disease and 190 patients with mUC. Among the 795 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 59 months). The most common (≥ 25%) adverse reactions were nausea (66%), diarrhea (65%), fatigue (62%), neuropathy (61%), anemia (54%), vomiting (59%), constipation (37%), decreased appetite (34%), rash (23%) and abdominal pain (28%).

Metastatic Triple-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label study (ASCENT, IMMU-132-05) in patients with mTNBC who had previously received a taxane and at least two prior therapies. Patients were randomized (1:1) to receive either TRODELVY (n=258) or single-agent chemotherapy (n=224) and were treated until disease progression or unacceptable toxicity. For patients randomized to TRODELVY, the median duration of treatment was 4.4 months (range: 0 to 23 months). Serious adverse reactions occurred in 27% of patients, and those in >1% included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients, including respiratory failure (1%), sepsis (1%), hemorrhagic (1%), and pulmonary hemorrhage (1%). The incidence of Grade 3-4 non-hematologic adverse reactions in patients treated with 4 cycles was similar among patients treated with or without TRODELVY. The most frequent (≥5%) adverse reactions leading to death in patients treated with TRODELVY were neutropenia (4%), diarrhea (5%), respiratory infection and neumocystosis (5%), vomiting (2%), and fatigue (4%). Adverse reactions leading to a dose reduction in ≥2% of patients were neutropenia (15%), diarrhea (11%), and fatigue (11%). C-SGF was used in 47% of patients who received TRODELVY. The most common adverse reactions (≥25%) were fatigue, neutropenia, diarrhea, nausea, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most common grade 3-4 adverse reactions (≥25%) were neutropenia (49%), decreased appetite (34%), and decreased lymphocytes (35%).

Locally Advanced or Metastatic Urothelial Cancer

The safety of TRODELVY was evaluated in a single-arm, open-label study (TROPHIM, IMMU-132-06) in patients (n=113) with mUC who had previously received platinum-based and anti-PD-1/PD-L1 therapy. Serious adverse reactions occurred in 44% of patients, and those in >1% included infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), sepsis or bacteremia (5%), diarrhea (4%), anemia, venous thromboembolism, and small intestinal obstruction (3% each), pneumonia, abd. pain, and thrombocytopenia (2% each). Fatal adverse reactions occurred in 3.5% of patients, including sepsis, respiratory failure, neutropenia, and completed suicide. TRODELVY was permanently discontinued for adverse reactions in 10% of patients. The most frequent of these adverse reactions was neutropenia (14%, including febrile neutropenia in 25%), infection (12%), and acute kidney injury (8%). The most common (≥25%) adverse reactions leading to a dose reduction in ≥2% of patients were neutropenia (15%, including febrile neutropenia in 3%), diarrhea (11%), fatigue (8%), and infection (4%). C-SGF was used in 47% of patients who received TRODELVY. The most common adverse reactions (≥25%) were diarrhea, fatigue, neuropathy, nausea, any infection, asthma, anemia, decreased appetite, constipation, vomiting, rash, and abdominal pain. The most common adverse reactions (≥25%) were diarrhea, fatigue, neutropenia, nausea, any infection, asthma, anemia, decreased appetite, constipation, vomiting, rash, and abdominal pain.
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