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—SUMIT MADAN, MD

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Case-Based Roundtable Meetings Spotlight

**Luciano J. Costa, MD, PhD**
Associate Director for Clinical Research
O’Neal Comprehensive Cancer Center
University of Alabama at Birmingham
Birmingham, AL

**Targeted Oncology™: What are the options for primary therapy in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM)? What is the role of transplant in these patients?**

**COSTA:** Transplant-eligible patients with NDMM were in the IFM 2009 study [NCT01191060], which was designed 12 years ago, when people were very impressed by the efficacy of RVd [lenalidomide (Revlimid), bortezomib (Velcade), dexamethasone].1,2 So they said, “Well, now that we have this great regimen, let’s see if we can postpone transplant without prejudice.”

They got transplant-eligible patients up to the age of 65, and everybody got 3 cycles of RVd, and [collection of] autologous stem cell transplant (ASCT) cells. Half the patients got ASCT followed by 2 cycles of RVd and the other half got RVd for 5 more cycles, making it 8 cycles. Beyond that, everybody received fixed-duration maintenance for 12 months with lenalidomide as a single agent. Upon progression, the patients on deferred transplant in the RVd alone arm, were to get an ASCT and indeed, 77% of them did. The primary end point was progression-free survival [PFS]. It was a positive trial, which showed that up-front transplant is superior to the deferred transplant and this was more prominent in the standard-risk patients.1,2

The IFM 2009 [PFS by MRD (minimal residual disease) status] study results were updated at the ASH [American Society of Hematology] 2020 annual meeting by Dr Perrot. The MRD was 10⁻⁶, the deepest level of MRD, and importantly, only about 30% of the patients on the transplant arm had MRD negativity, and only 20% in the RVd alone arm. Nevertheless, the group that achieved MRD negativity had outstanding results. Just keep in mind: These patients only got 1 year of maintenance, but if you look at patients 7 years after discontinued maintenance, you still have many alive without progression. But interestingly, even among MRD-negative patients, the ones who got there with transplant still do better. That’s also certainly true for the patients who were MRD positive with transplant.2

**How has transplant been investigated in more recent studies?**

The FORTE trial [NCT02203643] still informs the current role of transplant and takes it up a notch [by using] carfilzomib [Kyprolis], which is seen as perhaps a better...
proteasome inhibitor than bortezomib. This 3-arm study tried to answer 3 questions.³

First, what was the best partner for carfilzomib for these patients? Was it cyclophosphamide [Cytoxan] or lenalidomide? When a triplet is used with carfilzomib, does one still need transplant? So the options are KCd [carfilzomib, cyclophosphamide, dexamethasone], ASCT, KCd; KRd [carfilzomib, lenalidomide, dexamethasone], ASCT, KRd; or 12 cycles of KRd, essentially replacing transplant with 4 cycles of KRd. There was a second randomization between lenalidomide or carfilzomib [KR] plus lenalidomide alone [R] maintenance until progression or intolerance.³

I think this is the second or third study that confirmed that the best partner for proteasome inhibitors is an IMiD [immunomodulatory imide drug]. So the KRd plus ASCT arm did far better than the KCd plus ASCT arm. But also, and very importantly, KRd plus ASCT did far better than the [12 cycles of] KRd. So even when using 12 cycles of a triplet with carfilzomib, ASCT still outperformed conventional therapy, and that seems to be the case irrespective of staging or cytogenetic risk or LDH level at the time of presentation.³

The most intriguing part of this study is the second randomization [for maintenance therapy]. So those are people who made it to the end of those 12 cycles, or 4 cycles plus ASCT plus 4 more cycles. They got randomized again for R, very much like it is done in the United States, or KR maintenance. There was still a positive comparison that showed an improving PFS for patients who got doublet maintenance therapy, and the benefit, again, seems to go for different profiles of risk and not limited to particular patient groups.³ ⁴

What if monoclonal antibody therapy is incorporated?
The largest study done to date, [which is the phase 3 CASSIOPEIA study [NCT02541383]], used daratumumab [Darzalex], an anti-CD38 monoclonal antibody. It used a European paradigm where arm A had 4 cycles of VTd [bortezomib, thalidomide [Thalomid], and dexamethasone], transplant, and then 2 more cycles of VTd and compared that to arm B, which had the addition of daratumumab [D-VTd]. There was a second randomization for the maintenance phase that compared observation vs single-agent daratumumab every 8 weeks, which is very infrequent dosing, for 2 years [followed by observation until progression of disease].³ ⁵

It was a huge study with over 1000 patients. As they evolved to different phases of treatment, the responses got deeper, but certainly more in the D-VTd arm, which outperformed both arms in terms of the primary end point that was stringent CR [(complete response) at 29% for D-VTd vs 20% for VTd (P = .001)], but also in MRD-negative rates, and median PFS, which was [51.5 months for VTd and was not reached for D-VTd (HR, 0.58; 95% CI, 0.47–0.72; P < .0001)]. The overall survival [OS] hasn’t been reached on the interim analysis but it looks like it’s going to favor D-VTd.⁵

The data presented at the annual American Society of Clinical Oncology meeting in June 2021 generated a lot of discussion because of the maintenance phase of observation vs daratumumab for 2 years.⁶ It was a positive comparison. The arm that got daratumumab maintenance had almost a 50% reduction in the risk of progression or death.

Looking at the subsets, all the impact from daratumumab maintenance was for patients who had not received daratumumab during induction or consolidation. For that group, the reduction of risk [of progression] was gigantic at 68%, with a hazard ratio of 0.32 [95% CI, 0.23–0.46; P < .0001]. For patients who had already received daratumumab for induction and consolidation, continuing with it for maintenance did not seem to make any difference. The same was true for MRD negativity. There was a bit more MRD negativity with D-VTd plus daratumumab maintenance than D-VTd plus observation, but that was not sufficient to better PFS.⁶

Which regimen with daratumumab was investigated in the United States?
The best data we have so far with our standard regimen in the United States, which is VRd, was from the GRIFFIN study [NCT02874742]. It had a very similar eligibility criteria and study design. There were 4 cycles of RVd, ASCT, and 2 more cycles of RVd vs the same combination but with additional daratumumab. It also had 2 years of maintenance, but the difference is there was no second randomization. The RVd arm got R for maintenance and the D-RVd arm got D-R maintenance. It was a much smaller randomized phase 2 study with over 200 patients.⁷

Like in the CASSIOPEIA study, as you go through the phases of therapy, the responses become deeper and more frequent on both arms, but certainly more on the daratumumab-containing arm.

The subset analysis that was presented at the ASH 2020 annual meeting showed no clear tendency, although the high-risk subset seems to benefit less from the addition of daratumumab, but that’s a difficult group that tends to benefit less from just about any therapy introduced.⁸

The PFS and OS were both secondary end points. This study, it is important to remember, is not powered and mature to show differences in these outcomes. But interestingly, both PFS and OS remain extremely high for both arms.⁸ A more definitive trial is the randomized phase 3 PERSEUS trial [NCT03710603], with subcutaneous daratumumab plus VRd vs VRd alone. The data presented at the American Society of Clinical Oncology meeting in June 2021 generated a lot of discussion because of the maintenance phase of observation vs daratumumab for 2 years. It was a positive comparison. The arm that got daratumumab maintenance had almost a 50% reduction in the risk of progression or death. Looking at the subsets, all the impact from daratumumab maintenance was for patients who had not received daratumumab during induction or consolidation. For that group, the reduction of risk [of progression] was gigantic at 68%, with a hazard ratio of 0.32 [95% CI, 0.23–0.46; P < .0001]. For patients who had already received daratumumab for induction and consolidation, continuing with it for maintenance did not seem to make any difference. The same was true for MRD negativity. There was a bit more MRD negativity with D-VTd plus daratumumab maintenance than D-VTd plus observation, but that was not sufficient to better PFS. Which regimen with daratumumab was investigated in the United States? The best data we have so far with our standard regimen in the United States, which is VRd, was from the GRIFFIN study [NCT02874742]. It had a very similar eligibility criteria and study design. There were 4 cycles of RVd, ASCT, and 2 more cycles of RVd vs the same combination but with additional daratumumab. It also had 2 years of maintenance, but the difference is there was no second randomization. The RVd arm got R for maintenance and the D-RVd arm got D-R maintenance. It was a much smaller randomized phase 2 study with over 200 patients. Like in the CASSIOPEIA study, as you go through the phases of therapy, the responses become deeper and more frequent on both arms, but certainly more on the daratumumab-containing arm.

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So it is a very similar design to the GRIFFIN trial: 4 cycles, ASCT, 2 more cycles, then the patients who got the VRd continue R maintenance until progression. The groups that get D-VRd go with D-R for 24 months and are then assessed for MRD. If the MRD is negative they discontinue D and continue R; otherwise, they continue both agents. Every time an agent is added, there is an increase in toxicity. In the GRIFFIN study there was an increase in grade 3 and 4 neutropenia and an increase in thrombocytopenia. There has been a signaling in other trials of a little bit more infection, particularly upper respiratory infection.

CASE 2

- An 82-year-old White man presented to his primary care physician complaining of fatigue.
- Medical history: osteoarthritis, limited mobility
- Physical exam: pallor, hypertrophic changes at distal and proximal interphalangeal joints, poor grip strength, bilateral swelling in shoulder joints
- Initial blood work indicated anemia (hemoglobin: 10.2 g/dL), hypercalcemia (corrected calcium: 12.9 mg/dL), and elevated creatinine (1.5 mg/dL); creatine clearance: 50 mL/min
- The patient was referred to a hematologist for further evaluation.
- Peripheral blood smear showed rouleaux formation.
- Hemoglobin: 10.3 g/dL
- Creatinine: 1.5 mg/dL; creatinine clearance: 50 mL/min
- M-protein: 1.4 g/dL (immunofixation positive, IgG κ)
- Serum free light chains
  - κ free light chains: 144 mg/L
  - λ free light chains: 5 mg/L
  - Ratio: 29 (k/l)
- LDH: 186 U/L (elevated)
- β2-Microglobulin: 3.8 µg/mL
- Albumin: 3.5 g/dL
- Bone marrow biopsy: showed 43% plasma cells
- Fluorescence in situ hybridization: hyperdiploid

What are the options for primary therapy in transplant-ineligible patients with NDMM?
A trial that really informed our current choices include the SWOG-0777 trial [NCT00644228] that had patients with NDMM. It’s a little bit tricky because traditionally we look at trials in myeloma as being transplant eligible vs transplant ineligible, but this trial was a different population, because in the United States, we have patients with no immediate intent for transplant. So it captures patients who are transplant ineligible, but also some younger patients that, based on practice pattern, were not going to proceed with transplant. So it ended up being a much younger population than we see in the European transplant-ineligible trials.

Patients were randomized to the Rd arm for six 28-day cycles and the VRd arm for eight 21-day cycles. So the duration of therapy was 24 weeks for both arms. Both arms got maintenance with Rd at a dose of 25 mg and 40 mg, respectively. The patients continued to progression, unacceptable toxicity, or patient withdrawal. Less than half the patients were over the age of 65, which is quite interesting, but it was not truly a transplant-ineligible population. This study is significant, with improvement in PFS of 41 months for VRd vs 29 months for Rd [HR, 0.74; 95% CI, 0.59-0.92; P = .003]. Patients older than 65 did not seem to benefit.

The OS in this study is the reason why we are so attached to VRd in the United States, although I would argue we were already attached to it before this study. There was an improvement in [median OS, which was not reached for VRd vs 69 months for Rd (HR, 0.709; 95% CI, 0.543-0.926; P = .0114)]. Looking at age groups, the difference is mostly due to younger patients, but there’s not a discernible difference between Rd and VRd in patients 65 years and older.

For the toxicity profile there is more neurological toxicity, pain, sensory neuropathy, and gastrointestinal toxicity with VRd.

We love a regimen until there’s something better, then we start hating it. We have a little bit of a mixed relationship with bortezomib. It once was the savior of myeloma, but now it is the drug that everybody loves to hate, but I think the OS argument, which I think is a very strong one, needs to be taken with a big grain of salt among the older patients because the advantage is not so clear, and they have more toxicity.

How have other regimens been investigated in the transplant-ineligible space?
RVD Lite [NCT01782963], a published phase 2 study, had patients who were over 65 [or ineligible to transplant]. It was a relatively small study with 50 patients. I think every center has their own version of RVD Lite and ours is slightly different from this study, which used 15 mg of lenalidomide from day 1 to day 21; bortezomib, once weekly; and dexamethasone 40 mg twice weekly for patients younger than 75, and once weekly for patients older than 75. This was done for nine 35-day cycles followed by consolidation with less frequent dosing of both, and an optional maintenance phase [with lenalidomide until progression or

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I find it very intriguing that even though the SWOG-0777 trial had a younger and healthier population, the PFS of the control arm, which was Rd, was comparable if not even inferior to VRd, which was 41 months.”

—LUCIANO J. COSTA, MD, PHD

The results of the ENDURANCE study [NCT01863550] were published in 2020. The trial sought to see if outcomes of patients with NDMM without immediate intent for transplant [could be improved] by upgrading the proteasome inhibitor from bortezomib to carfilzomib. So the Rd arm is the same, but the proteasome inhibitor was either bortezomib at the traditional dosing, or carfilzomib 36 mg/m² twice weekly, for 3 weeks out of 4 for a total of 9 cycles. There was a second randomization trying to answer the optimal duration of maintenance, 2 years of lenalidomide vs indefinite lenalidomide, but we have no results yet.

With bortezomib there is more neuropathy, but with carfilzomib, there is more cardiovascular and renal toxicity. The overall response rates [ORR] were very similar at 84% for VRd vs 87% for KRd. The MRD negativity was a little bit higher in KRd, but to great disappointment, the PFS didn’t seem to change, and was about 34.5 months in both arms.

What were the results of adding daratumumab to treatment for these patients?

Another important study is the MAIA trial [NCT02252172] built on the prior standard, at least in most of the world, for transplant-ineligible patients with NDMM, which was lenalidomide and dexamethasone until progression.

This study asks whether adding daratumumab to the regimen until progression or intolerance improves outcomes. So this population was truly transplant ineligible, as defined in Europe. The patients were either older than 70 or younger than 70 with a contraindication for transplant. The median age was 73, almost a decade older than in the SWOG-0777 trial.

The outcomes were improved with the addition of daratumumab: 5-year PFS rate was 53% for D-Rd vs 29% for Rd, and the median PFS was not reached for D-Rd vs 34 months for Rd, with a hazard ratio of 0.53 [95% CI, 0.43-0.66; P < .0001]. The biggest update, a late-breaking abstract, came from the European Hematology Association in 2021 and showed, for the first time, a statistically significant improvement in OS. The 5-year OS rate went from 53% in Rd to 66% in D-Rd [HR, 0.68; 95% CI, 0.53-0.86; P = .0013] but the median OS has not been reached in both arms. Not surprising, there’s more frequent and deeper responses on the D-Rd arm with a higher proportion of patients with MRD negativity.

From the population level data, the median OS for patients with myeloma in the United States is about 6 years. Now, you have a population that’s older, transplant ineligible, with a 5-year PFS rate of 53% and a 5-year OS rate of 66%, which is quite impressive.

Of course, the common theme is adding a drug adds toxicity. For D-Rd, there is more neutropenia, particularly grade 3 and 4 going from 35% to 50%, but thrombocytopenia was about the same, and lymphopenia was a little bit more. Of course, you get infusion-related reactions from daratumumab of about 41% for any grade, but rarely grade 3 or 4. There is more pneumonia of any grade in the daratumumab arm, at 23% vs 13%, and grade 3 and 4 at 14% vs 8%. Certainly, there is a penalty to improving PFS and OS, in terms of a little bit more cytopenia and infections.

In summary, I find it very intriguing that even though the SWOG-0777 trial had a younger and healthier population, the PFS of the control arm, which was Rd, was comparable if not even inferior to VRd, which was 41 months. All these studies have different populations; they are hard to compare and they are about 1 decade apart. But I think when you look at the control arm of both studies, it shows that it is not too far fetched to compare the impact of adding a proteasome inhibitor vs the impact of adding an anti-CD38 monoclonal antibody.

The RVD-Lite study is right there in the middle; it doesn’t seem to have performed as well as the VRd, but it’s close at 35.1 months. The OS advantage for VRd from the SWOG 0777 trial showed a hazard ratio of 0.71 [95% CI, 0.54-0.93], and DRd, from the MAIA study had a hazard ratio of 0.68 [95% CI, 0.53-0.86].
Case-Based Roundtable Meetings Spotlight

CARBONE: In the NCCN [National Comprehensive Cancer Network] guidelines and in practice, the first step when you’re dealing with non–small cell lung cancer [NSCLC], especially nonsquamous disease, is molecular testing. In my practice, we would get a core biopsy like the one described, and we would do a tissue-based analysis. At my institution, it’s all done in house, and we get EGFR, ALK, ROS1, RET, and MET [results] within 5 days and NGS [results] within 2 weeks for MET, BRAF, and those kinds of things. We generally use liquid biopsies only to look for resistance alterations, if we get an outside referral with inadequate tissue, or [if it is an] uncommon situation of inadequate tissue locally.

KHASAWNEH: In my practice, we contract with a commercial lab, Integrated Oncology, for NGS, and it takes about 3 to 4 weeks. So when I see patients, my approach is a bit different because of the practice. I do both liquid and tissue biopsy, because to get the liquid faster, I can use FoundationOne liquid biopsy and send tissue for NGS, waiting for the molecular markers to come. Whichever comes first with the answers that I’m looking for, I will use to make decisions for the patients.

continued on page 18
LENVIMA + everolimus is the only TKI-mTOR inhibitor combination following anti-angiogenic therapy in advanced RCC

**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 \( \geq 160 \text{ mmHg} \) occurred in 29% of patients, and 21% had diastolic blood pressure \( \geq 100 \text{ mmHg} \). In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

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

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

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

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

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

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

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

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

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

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

**Diarrhea.** Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrheas. 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
14.6-month median PFS: with LENVIMA + everolimus vs everolimus alone

<table>
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<th>Time (months)</th>
<th>Number of subjects at risk</th>
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<tr>
<td></td>
<td>LENVIMA + everolimus</td>
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<td>51</td>
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<td>12</td>
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<td>18</td>
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</tbody>
</table>

- 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
  - Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus

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

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

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 >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In RCC, QT interval increases >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 1A and 3 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 to learn more.
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 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, decoumarin, 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 organogestation at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Adverse Reactions

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

Use in Specific Populations

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

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC (endometrial carcinoma) and severe (CLcr ≤15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with 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. There is no recommended dose for patients with HCC 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.


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AFINITOR [package insert] label change.
LENVIMA® (lenvatinib) capsules BRIEF SUMMARY – See package insert for full prescribing information.

### Dosage 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.
- RCC: The recommended dosage is based on actual body weight: 12 mg orally once daily for patients greater than or equal to 60 kg or 8 mg orally once daily for patients less than 60 kg.
- HCC: The recommended dosage is 40 mg orally once daily.

**Combination Therapy:**
- 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 with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
- HCC: The recommended dosage is 80 mg orally once daily with everolimus 5 mg orally once daily.

**Dosage Adjustments 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 reductions of 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>Dose Adjustments for LENVIMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Grade 3</td>
<td>Withhold for Grade 3 that persists despite optimal antihypertensive therapy. Resume at reduced dose if hypertension is controlled at less than or equal to Grade 2.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Cardiac Dysfunction</td>
<td>Grade 3</td>
<td>Withhold until improved to Grade 0 or 1 baseline. Resume at reduced dose or discontinue depending on the severity and persistence of adverse reaction.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Arterial Thromboembolic Event</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Hemoptotaxis</td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue for hemoptotaxis.</td>
</tr>
<tr>
<td>Renal Failure or Impairment</td>
<td>Grade 3 or 4</td>
<td>Withhold until improved to Grade 0 or 1 baseline. 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 g of proteinuria per 24 hours. Resume at a reduced dose. Discontinue for nephrotic syndrome.</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Fistula Formation</td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Greater than 500 ms or greater than 60 ms increase from baseline</td>
<td>Withhold until improves to less than or equal to 488 ms or baseline. Resume at a reduced dose.</td>
</tr>
<tr>
<td>Reversible Posterior Leukoencephalopathy Syndrome</td>
<td>Any Grade</td>
<td>Withhold until fully resolved. 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</td>
<td>Withhold until improved to Grade 0 or 1 baseline. Resume at a reduced dose.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 laboratory abnormality</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 adverse reaction</td>
<td>Permanently discontinue.</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**
- **Hypertension**
  - Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 17 days (SELECT DTC) and 16 days (REFLECT HCC).
  - Grade 3 hypertension occurred in 44% of patients in SELECT (DTC) and in 24% in REFLECT (HCC).
  - Grade 4 hypertension occurred in 7% of SELECT (DTC) and 10% in REFLECT (HCC).
  - In patients receiving LENVIMA 18 mg orally once daily with everolimus in study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days.
  - Withhold hypertension in patients who have had an arterial thromboembolic event within the previous 6 months.

- **Cardiac Dysfunction**
  - Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 789 patients with DTC or RCC, HCC or RCC, Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, cardiac failure, venous thromboembolism, or death in left or right ventricular ejection fraction of more than 20% from baseline) occurred in 3% of LENVIMA-treated patients.
  - Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA if deterioration of cardiac dysfunction occurs.

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

- **Hepatotoxicity**
  - Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than RCC, serious hepatic adverse events occurred in 14% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatic encephalopathy, occurred in 0.5% of patients.

- **Renal Failure or Impairment**
  - Renal impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients in REFLECT (HCC).
  - Grade 3 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatality in each study.

- **Proteinuria**
  - Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of patients in REFLECT (HCC). Two percent of patients discontinued LENVIMA and 0.2% discontinued sorafenib due to proteinuria.

- **Gastrointestinal Perforation**
  - Gastrointestinal perforation occurred in 0.5% of patients receiving LENVIMA in SELECT (DTC) and in 0.2% of patients in REFLECT (HCC).

- **Fistula Formation**
  - Fistula formation occurred in 1% of patients receiving LENVIMA in SELECT (DTC) and in 0.2% of patients in REFLECT (HCC).

- **QT Prolongation**
  - QT prolongation occurred in 11% of patients in SELECT (DTC) and in 5% of patients in REFLECT (HCC). Grade 1 prolongation occurred in 11% and in 5% of patients in SELECT (DTC) and in 8% and in 3% of patients in REFLECT (HCC), respectively. In Study 205 (RCC), prolongation occurred in 31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 prolongation occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus.
  - Monitor for prolongation prior to initiating LENVIMA and periodically during treatment. If urine dipstick proteinuria greater than or equal to 1+ is detected, obtain 24 hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

- **Diabetes**
  - Of the 737 patients treated with LENVIMA in SELECT (DTC) and REFLECT (HCC), diabetes occurred in 43% of patients, including Grade 3 diabetes in 6%.
  - In Study 205 (RCC), diabetes occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 diabetes. Diaphragm was the most frequently cause of dose interruption and diabetes occurred despite dose reduction.

---

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

The most common adverse reactions observed in LENVIMA-treated patients (≥30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dyspnea. The most common serious adverse reactions (at least 2%) were hypertension, fatigue (5%), hypocalcemia (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 88% of patients receiving LENVIMA; 18% of patients discontinued LENVIMA for adverse reactions. The most common adverse reactions at least 5% resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions at least 1% resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

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

**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 (DTC)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 24 mg N=261</th>
<th>Placebo N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>73</td>
<td>44</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>29</td>
<td>0.4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Oral pain</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67</td>
<td>35</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>62</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>54</td>
<td>18</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Urinary System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Nephrotic or renal insufficiency</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 24 mg Grades 3-4 (%)</th>
<th>Placebo Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (AST)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase (ALT)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinically important adverse reactions occurring more frequently in LENVIMA-treated patients than patients receiving placebo (but with an incidence of ≥2%) were hypocalcemia (9%), hyperkalemia (6%), hypertension (5%), and dehydration (3%).

Laboratory abnormalities with a difference of ≥2% in Grade 3-4 events and at a higher incidence in the LENVIMA arm are presented in Table 4.
Clinical relevant adverse reactions (<20%) that occurred in patients receiving LENVIMA/pembrolizumab were myocardial infarction (3%) and angina pectoris (1%).

### Table 5: Adverse Reactions in >20% 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>Blood Glucose</td>
<td>66</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Potassium</td>
<td>42</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Phosphate</td>
<td>33</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Calcium</td>
<td>41</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hyperuricemia</td>
<td>14</td>
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<td>Hyperlipidemia</td>
<td>13</td>
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<td>0</td>
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<td>Hypercalciemia</td>
<td>12</td>
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<td>Hyperkalemia</td>
<td>11</td>
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<td>0</td>
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<td>Hypernatremia</td>
<td>10</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Hypoglycemia</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8</td>
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Table 7: Adverse Reactions Occurring in ≥10% of Patients in the LENVIMA with Everolimus Arm in Study 205 (HCC)

<table>
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<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=62</th>
<th>Everolimus 10 mg N=50</th>
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<td>Respiratory, Thoracic and Mediastinal</td>
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<td>Cough</td>
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<td>Dyspnea/Epistaxis</td>
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<td>Dysphoria</td>
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<tr>
<td>Skin and Subcutaneous Tissue</td>
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<tr>
<td>Vascular</td>
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<td>Hypertension/Increased blood pressure</td>
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<td>Hemorrhagic events^</td>
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<td>Hemoptysis</td>
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<td>21</td>
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<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=260 to 473</th>
<th>Everolimus 10 mg N=278 to 470</th>
</tr>
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<tbody>
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<td><strong>Laboratory Abnormality</strong></td>
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</tr>
<tr>
<td><strong>Chemistry</strong></td>
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<tr>
<td>Hyperglycemia</td>
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<td>12</td>
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<tr>
<td>Hypokalemia</td>
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<td>6</td>
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<td>Hypophosphatemia</td>
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<td>Hypocalcemia</td>
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<tr>
<td>Increased aspartate aminotransferase (AST)</td>
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<tr>
<td>Increased alanine aminotransferase (ALT)</td>
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<tr>
<td>Increased alkaline phosphatase</td>
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<td>Increased creatine kinase</td>
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<td>Anemia</td>
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<tr>
<td>Neutropenia</td>
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</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=260 to 473</th>
<th>Everolimus 10 mg N=278 to 470</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Abnormality</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
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<tr>
<td>Hyperglycemia</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Increased Eosin</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hyperchloremic Blood</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
<td>6</td>
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<tr>
<td>Hypophosphatemia</td>
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<td>2</td>
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<tr>
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<td>Increased alanine aminotransferase (ALT)</td>
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<tr>
<td>Increased alkaline phosphatase</td>
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<tr>
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</table>

In Table 10, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA with everolimus arm are presented.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 18 mg/12 mg N=476</th>
<th>Sorafenib 800 mg N=476</th>
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<tbody>
<tr>
<td>Renal and Urinary</td>
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</tr>
<tr>
<td>Proteinuria/Urine protein present</td>
<td>18</td>
<td>10</td>
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<tr>
<td>Hyperkalemia</td>
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<tr>
<td>Hyperuricemia</td>
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<td>17</td>
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<tr>
<td>Increased creatine kinase</td>
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<td>17</td>
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</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 18 mg/12 mg N=476</th>
<th>Sorafenib 800 mg N=476</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
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<td>Hyponatremia</td>
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<td>10</td>
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<tr>
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</tbody>
</table>

In Table 11, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the sorafenib arm are presented.

Table 11: Grade 3-4 Laboratory Abnormalities Occurring in ≥2% of Patients in the Sorafenib Arm in REFLECT (HCC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Sorafenib 800 mg N=476</th>
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<tbody>
<tr>
<td><strong>Chemistry</strong></td>
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<td>Hyperglycemia</td>
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</tbody>
</table>

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

Table 12: Grade 3-4 Laboratory Abnormalities Occurring in ≥2% of Patients in the Sorafenib Arm in REFLECT (HCC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Sorafenib 800 mg N=476</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>10</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>10</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>10</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>10</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10</td>
</tr>
<tr>
<td>Increased creatine kinase</td>
<td>10</td>
</tr>
</tbody>
</table>
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>Adverse Reaction</th>
<th>All Grades* (%)</th>
<th>Grades 3-4 (%)</th>
<th>All Grades* (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidia 1</td>
<td>67</td>
<td>0.9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>38</td>
<td>6</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25</td>
<td>2.6</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>58</td>
<td>11</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>8</td>
<td>20</td>
<td>2.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48</td>
<td>2.9</td>
<td>47</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>7</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>34</td>
<td>10</td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>50</td>
<td>6</td>
<td>34</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>2.3</td>
<td>4.9</td>
<td>0</td>
</tr>
</tbody>
</table>

*Graded per NCI CTCAE v4.03

1 Includes hypothyroidism, blood thyroid stimulating hormone increased, thyrotoxic, primary hypothyroidism, and secondary hypothyroidism
2 Includes hypertension, blood pressure increased, hypertension, hypertensive encephalopathy, and blood pressure fluctuation
3 Includes epistaxis, vaginal hemorrhage, hematoma, gingival bleeding, menorrhagia, rectal hemorrhage, constipation, hemorrhage, central hernia, conjunctival hemorrhage, hemorrhage, uterine hemorrhage, urinary tract lower gastrointestinal hemorrhage, menorrhagia, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, intracranial hemorrhage, stroke, injection site hemorrhage, menorrhagia, petechiae, site hemorrhage, upper gastrointestinal hemorrhage, bleeding, upper gastrointestinal hemorrhage, bleeding, umbilical hemorrhage, umbilical hernia, varicose vein, and rectal hemorrhage
4 Includes fatigue, asthenia, malaise, and lethargy
5 Includes diarrhea and gastrenteritis
6 Includes stomatitis, mucosal inflammation, epistaxis, purpura, upper, ulcer, ulcer, chilblain, oral mucosal erythema, and tongue ulceration
7 Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, and epigastric discomfort
8 Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw
9 Includes decreased appetite and early satiety
10 Includes proteinuria, protein urine present, hemoglobinuria
11 Includes urinary tract infection, cystitis, and pyelonephritis
12 Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, and skin reaction
13 Includes rash, rash maculo-papular, rash papular, rash urticarial, rash macular, rash papular, rash papular, rash vesicular, and application site rash

Table 12: Laboratory Abnormalities Worsened from Baseline* Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>All Grades* (%)</th>
<th>Grades 3-4 (%)</th>
<th>All Grades* (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine Carcinoma (not MSI-H or dMMR)</strong></td>
<td>LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342</td>
<td>Doxorubicin or Paclitaxel N=325</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Dose interruptions of LENVIMA due to an adverse reaction** occurred in 58% of these patients. The most common (≥2%) adverse reaction leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), palmar-plantar erythrodynesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthma (5%), and weight decreased (5%).

Postmarketing Experience The following adverse reactions have been identified during post approval use of LENVIMA. Based on the available evidence, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: pancreatitis, increased amylase

General: increased wound healing

Hepatobiliary: cholelithiasis

Renal and Urinary: nephrotic syndrome

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

**DRUG INTERACTIONS**

**Very Severe Drug-Drug Interactions**

1. **Coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval.**

2. **Drug interactions that result in drug exposure increases.**

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

**Data**

**Animal Data**

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses ≥0.3 mg/kg (approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)) to pregnant rabbits resulted in gestational and postnatal losses and reductions in body weight gain, fetal body weight, and fetal survival. In the rabbit, the maternal body weight gain was decreased at the highest dose level of 0.5 mg/kg (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA). There was a significant increase in the proportion of rabbits with fetal abnormalities.

**Contraception**

Females and Males of Reproductive Potential

**Pregnancy**

**Risk Summary**

It is unknown whether LENVIMA is present in human milk; however, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma. Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment with LENVIMA and for at least 1 week after the last dose.

**Data**

**Animal Data**

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

**Lactation**

**Risk Summary**

There is no available human data informing the drug-associated risk.

**Drug-Lactation Interactions**

**Pedia**
Geriatric Use

Of the 261 patients with differentiated thyroid cancer (DTC) who received LENVIMA in SELECT, 45% were ≥65 years of age and 11% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 352 patients with renal cell carcinoma (RCC) who received LENVIMA with pembrolizumab in CLEAR, 45% were ≥65 years of age and 13% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Of the 82 patients with RCC who received LENVIMA with everolimus in Study 205, 36% were ≥65 years of age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between these 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 80-89 mL/min) or moderate (CLcr 60-89 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. 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 evenolimus 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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CARBONE: Yes, I think that’s a very reasonable approach. We usually use another platform, but we often get our results back within 4 or 5 days, which is remarkably fast and very easy.

TEJWANI: In our institution, the turnaround time in house is at least 2 weeks, so we’ll end up sending to FoundationOne or Tempus, but I wish the turnaround time was better. Five days is great.

CARBONE: That is a limiting factor with these patients.

TEJWANI: We are doing the PD-L1 and PD-1 markers in house.

CARBONE: Do both of you use a commercial platform, so you get the MET exon 14, BRAF mutations, NTRK, and all of those?

TEJWANI: Yes.

CARBONE: Anybody else have a different approach?

KUMAR: I’ve sent for a Tempus panel, so both solid and liquid. Usually, we have to wait for at least 2 weeks before we can even start any targeted therapy.

CARBONE: I think we all are faced with patients with a new diagnosis who want treatment to start right away, so that 2 weeks seems like forever. Do you ever have difficulty convincing patients to wait for their testing?

KUMAR: There are some patients who cannot wait, are symptomatic. I start with a chemotherapy combination, and when I get the NGS panel then, [if appropriate, I start] immunotherapy [IO].

CARBONE: [It’s interesting] to see that a lot of [you] are sending both liquid and tissue at the same time. It does seem like there’s a redundancy there. It’s like getting a brain MRI and a head CT at the same time.

KUMAR: No, [for us] Tempus doesn’t run the liquid unless there’s inadequate tissue. So we save some time.

AL BAGHDADI: We use FoundationOne when there’s sufficient tissue. It takes about 2.5 weeks to come back. We don’t do concomitant liquid biopsies unless the tissue was inadequate, and we wait. Our pathologist would rather stay away and not run any testing on these patients. They started out with doing EGFR and ALK testing, and as the number of these mutations increased, they stayed out of it. If the patient requires immediate treatment, where they can’t wait 2.5 weeks, I give 1 cycle of carboplatin- or cisplatin-based doublet treatment without immune checkpoint inhibition while waiting for the test results.

CARBONE: That’s a very logical approach. I think the biggest mistake is using an IO in someone that you then want to switch immediately to osimertinib [Tagrisso], because of the possible complications and lack of benefit of IO in that setting. Sometimes I can’t get a pembrolizumab [Keytruda] approval immediately, and I want to start right away, so I’ll start with the chemotherapy alone with cycle 1.

MAHAJAN: At Case Western Reserve University in Cleveland, Ohio, the [tissue biopsy] is done by the in-house pathologist, and they have expanded their lung panel—they’ve been checking both DNA- and RNA-based testing. That’s helpful because not only does it get done in house but it’s also part of the same pathology report. So you don’t have to log into different portals to get different results. The same report also has PD-L1 expression and microsatellite instability testing.

The problem, even in house, is the turnaround time, especially if you are in ambulatory setting or a satellite hospital. In those situations, sometimes you’re on your own; you may order a liquid biopsy with Guardant or something similar just for the timing. But [having] a more comprehensive report where everything is included really helps with patient care.

CARBONE: I agree. I’ve been working on trying to go 1 step further and having molecular reported just like any other laboratory tests in the EPIC system. I get messages and alerts in my inbox if I get a potassium [result] that’s 0.1 out of range. And yet, if I have a patient with an ALK fusion, I never get an alert in my inbox. We now have EGFR, ALK, ROS1, and RET in our EPIC system; all those things show up in the same laboratory panel as a complete blood count or a chemistry panel would. And we can just click on them to see which variant or whether it’s wild type. But still, it doesn’t alert me if it’s abnormal. I think EPIC is working toward a better integration of all the different molecular platforms, but I think it should be presented that way.

NEMUNAITIS: You’re saying if there is an EGFR mutation, they alert you that there was a mutation found?

CARBONE: EPIC shows it in the laboratory panel, but right now EPIC doesn’t alert me. But I’ve trained our molecular pathologist to page us if it comes back positive. So if we get a new EGFR result, I’ll get a page saying, “Jane Smith has an EGFR L858R.”
NEMUNAITIS: That’s great. I have patients with immune thrombocytopenic purpura, and I get paged every month because [their result is] still low [after] 5 years, but I agree, that’s amazing.

CARBONE: The impact of potassium at 3.2 mmol/L is way less than that of an ALK fusion mutation in a newly diagnosed patient. So you would think that they would notify you.

DISCUSSION QUESTION
Would you use stereotactic radiosurgery (SRS) for this patient?

CARBONE: How many of you would do SRS for an asymptomatic brain metastasis in this setting or try up-front therapy? Would you just treat with systemic therapy, or would you radiate for a 2-cm, asymptomatic brain metastasis?

KUMAR: I would stay with systemic therapy and still get the opinion from the radiation oncologist.

AL BAGHDADI: I would have the radiation oncologist see them, and probably use CyberKnife radiosurgery. At 2 cm—if it was smaller than that, I would start with systemic therapy for sure.

WINTER: [As a] radiation opinion, 2 cm is an interesting cutoff point for us. When we get above 2 cm, we usually have to go with a lower dose level. The control is not as good with SRS once you get above the 2-cm mark because you have to dose reduce. There are some strategies that you can use to address that, such as a staged approach, where you bring the patient back a month later and give a second dose. But if you can avoid having to do that, it’s definitely beneficial.

That being said, I recognize that a lot of the targeted agents and IO agents have intracranial efficacy. To the extent that we can avoid radiotherapy and only treat if needed, I’m all for that. I think it’s an individualized decision. In this patient I’d probably, with all else being equal, lean toward it just because of the size.

CARBONE: If [the patients] were symptomatic and required steroids, then that would be a reason for radiation, trying to get them off steroids before IO. Or if there were 25 metastases but [the patient was] still asymptomatic, you could do a trial of the IO therapy. I’ve seen very good central nervous system [CNS] responses to IO, but I’ve also seen a lot of CNS-only relapses with IO—systemic control, but CNS relapses. It’s unclear. But with the targeted therapies, I’ve seen durable long-term control

with multiple brain metastases with no radiation with ALK or EGFR.

POLLING QUESTION
“Next-generation sequencing was negative for molecular aberrations in EGFR, ROS1, BRAF, ALK, RET, MET, ERBB2, NTRK, and KRAS. What would be your preferred recommendation for this patient?”

| Platinum doublet chemotherapy | 67% (10) |
| Single-agent PD-L1 therapy | 33% (5) |
| Dual immune checkpoint blockade with anti–PDL1/anti–CTLA-4 | 0% (0) |

TOTAL VOTES: 15

CARBONE: My answer was single-agent PD-L1 therapy. You could argue why you should use doublet and why you should use single agent. I believe the data show they’re fairly equivalent in this population, and that chemotherapy is effective as a second-line agent if you need it. But I have multiple patients who have never had chemotherapy, just single-agent IO, and are doing fine 5, 6, 7 years later.

Many [clinicians] choose a platinum doublet because they say the response rate is a little higher. What is the rationale you would use?

CHOWDHARY: Unless a patient is older or absolutely refuses chemotherapy, are there any other factors that would weigh in? I’ve tended to do both chemotherapy and IO. I think you’re right—the vast majority of experts do feel that with a PD-L1 level of greater than 50%, IO alone is sufficient.

There is a meta-analysis that pooled data from different trials in patients with PD-L1 50% or higher. They were looking at patients who received IO alone or chemotherapy/IO in this particular patient population….We’ve known that the response rates are higher, but for IO alone they’re roughly between 45% to 48%. With chemotherapy/IO, they can be as high as 60% to 63%.

There was no survival benefit seen, but because the response rate was higher, and even the progression-free survival was trending better as well. I’ve still tended toward using chemotherapy/IO if a patient is relatively fit and understands that there may be no survival benefit. That’s why I’ve chosen that more often.

CARBONE: You have to understand that in a retrospective analysis such as that, often a real-world analysis, it’s the fitter patients who get chemotherapy/IO and the less fit ones who get single agent. So they would tend to...
do better just from that parameter alone. You say there’s no survival benefit. I don’t look at response rates so much [or] median survival so much when I look at these curves. My gold standard is landmark survival; 3-, 4-, 5-year landmark survival, how many patients are alive at that point.

The 3-year landmark survival for KEYNOTE-189 [NCT02578680] vs KEYNOTE-024 [NCT02142738] was the same, so why give chemotherapy if it’s not doing anything?

If you give maintenance pemetrexed [Alimta], you’re giving steroids, and you do have edema issues with the chronic pemetrexed. So that’s another issue in my mind.

TEJWANI: Would you comment on high volume, as it is mentioned? You said that response rates don’t matter, but this patient had liver and lung lesions, adrenal and brain; would you weigh in on the patient populations where you would use chemotherapy with IO?

CARBONE: If it’s bulky and overt superior vena cava syndrome or something similar—we don’t have the scans here, but a 9-cm lesion can be in the lung parenchyma and not causing any problems. But a smaller one in the wrong place can cause big problems.

It’s uncommon for me to use chemotherapy/IO in the first line unless there’s an urgent issue and I need a response.

AL BAGHDADI: How about emerging data about the magnitude of benefit from IO vs chemotherapy being better in patients who have KRAS mutation rather than KRAS wild-type, which is the case for this patient?

There are also a few cancers out there where significant or extensive liver metastases have been associated with worse survival when you do IO alone. These 2 issues sway me toward chemotherapy/IO, and if I use carboplatin/pemetrexed, I stop chemotherapy after 4 cycles—both drugs—if I achieve a good response.

CARBONE: Yes, that’s the way to do it. That’s not the way the study did it. If you are worried about the liver metastases, IMPower150 [NCT02366143] showed that patients with liver metastases did better; that’s with the bevacizumab [Avastin] combination.

So again, we’re relying on cross-trial comparisons. There is a clinical trial ongoing, INSIGNA [NCT03793179], that is randomizing patients between pembrolizumab monotherapy and pembrolizumab/chemotherapy. That has 300 patients enrolled already, and so potentially that will help us. We’ve spent decades matching tyrosine kinase inhibitors to driver mutations; it’s unsatisfying to me to just use one size fits all for IO when we know that different patients have different markers.

POLLING QUESTION

“Which ICI are you most likely to recommend for this patient?”

<table>
<thead>
<tr>
<th>ICI</th>
<th>Percentage</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>100%</td>
<td>15</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Cemiplimab</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Platinum-based chemo</td>
<td>0%</td>
<td>0</td>
</tr>
</tbody>
</table>

TOTAL VOTES: 15

CARBONE: It’s a landslide: Pembrolizumab wins, and that’s not surprising. Physicians are comfortable with pembrolizumab. It had a bunch of early successes in phase 3 trials with impressive results. [Physicians] have been using it for years, and it’s not surprising to me that it has the majority of the market share.

I think there is a concern about liver metastases, but as far as which IO to use in an IO monotherapy setting, pembrolizumab has 3- and 6-week interval dosing—I usually start at 3 weeks to keep a closer eye on the patient, but if they’re stable and responding without toxicity, I’ll go to the 6-week schedule, which is convenient for a patient. Any comments on factors that influence your decision?

NAGASAKA: Is there a scenario when you would consider atezolizumab [Tecentriq] or cemiplimab [Libtayo]? Because as you just mentioned, I go straight to pembrolizumab, especially for the [dosing] reason.

CARBONE: The thing with cemiplimab is it looks great, but we just don’t have the long-term experience with it. Atezolizumab is known to have higher incidence of anti-drug antibodies, and a lot of the point estimates with atezolizumab are lower than pembrolizumab in multiple studies. So in this setting, I would go with pembrolizumab for all the reasons we talked about.

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So again, we’re relying on cross-trial comparisons. There is a clinical trial ongoing, INSIGNA [NCT03793179], that is randomizing patients between pembrolizumab monotherapy and pembrolizumab/chemotherapy. That has 300 patients enrolled already, and so potentially that will help us. We’ve spent decades matching tyrosine kinase inhibitors to driver mutations; it’s unsatisfying to me to just use one size fits all for IO when we know that different patients have different markers.

CHOWDHARY: In the end, for the vast majority of these various PD-1/PD-L1 inhibitors as single agents in [PD-L1]-high-expressing patients, I think the median survivals are pretty consistent with each other. I know pembrolizumab was first past the goal post, and probably has the most magnitude of data, even though hazard ratios are pretty similar. The magnitude of data serve pembrolizumab a lot
more in why it’s adopted so much. There’s a lot of experience with it now.

But if you look at the median survivals, they are very similar, in that 22- to 25-month period. That seems to be the median survival for most of these immune therapies in these PD-L1–high expressors. KEYNOTE-001 [NCT01295827] had mature 5-year survival rate data, and these patients who are either treatment naive, or in second/third line were treated with single-agent pembrolizumab. In treatment-naive patients, the 5-year survival was approximately 23% and in patients that had treatment before it was approximately 15%. But those are still very compelling 5-year survival rates, and some are even quoting survival rates of up to 30%.

What leads you not to choose pembrolizumab if you’re using it as a single agent in these high expressors? When do you use cemiplimab or something else, if you ever do that, in place of pembrolizumab?

CARBONE: Personally, I wouldn’t use anything else at this point. What might drive me to do that is if cemiplimab data matured, the data showed it was identical, it was one-fourth of the price, or somebody had a huge copay with pembrolizumab, for example. But that’s typically not the case; they price these things within 10% of each other. So that’s not an issue. Right now, the only time I would use something else is in the context of a trial.

AL BAGHDADI: I look at hazard ratio as being close, and maybe these drugs are interchangeable, because even KEYNOTE-024 looked a little better than the KEYNOTE-042 [NCT02220894], if you look at the population with PD-L1 of 50% or higher. They’re both using the same drug. So I don’t look at minor differences between the hazard ratios.

But cemiplimab and pembrolizumab are PD-1 inhibitors, whereas atezolizumab is [for] PD-L1. There are some retrospective data showing that PD-L1 inhibitors cause less pneumonitis. Is that something you see? In my clinic, I see more pneumonitis with atezolizumab and durvalumab [Imfinzi], because that’s what we use for small cell lung cancer, and I believe it’s the disease more than the drug. But there are some data out there arguing it’s less with PD-L1 inhibitors.

CARBONE: Yes, I think there are hints that there are differences. It’s interesting that the 2 approved regimens in small cell are both PD-L1 inhibitors, and the PD-1s haven’t done so well. Maybe for different diseases, a PD-L1 might be better. We just finished a neoadjuvant trial with PD-L1 atezolizumab and had good outcomes in that study.

So who knows? I have no objective reason to decide between the 2 right now, and they’ve never been compared head to head. I’ve seen lots of pneumonitis with the PACIFIC regimen [of durvalumab (NCT02125461)], for example, though that’s in a different context. I’m not sure that there’s a major difference in pneumonitis between them.

MAHAJAN: We have used these drugs from head to toe, from squamous cell skin cancer to lung cancer to endometrial cancer. My experience is they’re all the same. It depends upon what your combination is, whether it’s a tyrosine kinase inhibitor, IO, or chemotherapy—whichever you can get approved and whichever is more convenient for the patient. We have been looking for answers, from renal cell to hepatocellular carcinoma. I think [if] 1 study shows a little bit better results, it’s not because the agents are different, it’s just the way the study was designed and then done.

CARBONE: And how the patients happened to be chosen. So you’re in the “Coke vs Pepsi” camp here.

Cemiplimab is only approved for patients with greater than 50% PD-L1 expression—same with atezolizumab, but pembrolizumab has the greater than 1% approval, even though the subset analysis showed no benefit. They have different dosing. As I said, pembrolizumab has an every-6-week dosing.

REFERENCES


INDICATION AND USAGE

ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Effusion and Edema

Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%.

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

Myelosuppression

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

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

Infections

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

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

Cutaneous Reactions

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

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Cutaneous Reactions (continued)

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

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain. In LOTIS-2, serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion. Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

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

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

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

CONTRAINDICATIONS
None

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

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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. The cytotoxic component of ZYNLONTA, with loncastuximab tesirine-lpyl. 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 occurring in ≥2% of patients 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 ≥2% 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>Adverse Reaction</th>
<th>ZYNLONTA (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>30</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>23</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
</tr>
</tbody>
</table>
ADVERSE REACTIONS, including laboratory abnormalities, were thrombocytopenia, decreased hemoglobin, decreased glucose, increased aspartate aminotransferase (AST), and increased gamma-glutamyltransferase (GGT).

In this pooled safety population of 215 patients, the most common (>20%) adverse reactions were pruritus (32%), rash (28%), decreased appetite (23%), constipation (21%), nausea (19%), diarrhea (17%), and fatigue (15%).

58% receiving three or more cycles and 30% receiving five or more cycles. The median number of cycles was 3 (range 1 to 15) with 0.15 mg/kg in 215 patients with DLBCL in studies ADCT-402-201 (LOTIS-2) and ADCT-403-202 (LOTIS-3).

Myelosuppression

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

- **Blood and lymphatic system disorders**: Febrile neutropenia (3%)
- **Cardiac disorders**: Pericardial effusion (3%)
- **Infections**: Pneumonia (5%), sepsis (2%)
- **Skin and subcutaneous disorders**: Hyperpigmentation (4%)
- **General disorders**: Infusion site extravasation (<1%)

Clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA included:

- Blood and lymphatic system disorders: Febrile neutropenia (3%)
- Cardiac disorders: Pericardial effusion (3%)
- Infections: Pneumonia (5%), sepsis (2%)
- Skin and subcutaneous disorders: Hyperpigmentation (4%)
- General disorders: Infusion site extravasation (<1%)

Selected Other Adverse Reactions

- Inflammatory-related conditions were reported in 3% of patients in LOTIS-2, including pericarditis, pneumonia, pleuritis, and dermatitis.

Table 2 summarizes the laboratory abnormalities in LOTIS-2.

### Table 2: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYNLONTA* All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>57</td>
<td>21</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>AST increased</td>
<td>41</td>
<td>&lt;1&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
<td>&lt;1&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALT increased</td>
<td>34</td>
<td>3</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value.

**No Grade 4 adverse reactions occurred**

### Immunogenicity

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

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

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

**Risk Summary**

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

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

#### Data

**Animal Data**

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-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 embryo toxicity 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 Adverse women of reproductive potential to use effective contraception during treatment and for 9 months after the last dose.

**Males**

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

#### Infertility

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

**Pediatric Use**

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

**Geriatric Use**

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

**Hepatic Impairment**

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

Roundtable Discussion: Finn Discusses Options in HCC Treatment

CASE SUMMARY

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

DISCUSSION QUESTIONS

• Why might you choose biopsy for this patient?
• Would your use of biopsy be different if the patient did not have cirrhosis?
  ◦ Would it differ if the lesion was LR4?
• Assuming that a biopsy confirmed hepatocellular carcinoma (HCC), would you suggest additional genetic analyses on the tissue?
• Would you recommend any additional imaging?

SNEDDEN: I think the history of Crohn disease is certainly something to consider. Yes, the LI-RADS score is 5, but [I would] want to make sure it’s not colorectal cancer. So, that would be one of the main reasons I would consider the biopsy.

FINN: That’s a good thought, [because] chronic inflammatory disease of the colon is obviously associated with an increased risk of colon cancer.

JANA: Biopsy tends to have a high false-negative [result] and can cause considerable confusion in this setting when you have strong imaging confirmation and elevated AFP. That’s why I [would choose] no biopsy.

FINN: So does this patient need any further imaging? Or are you satisfied with [the CT scan of the] chest, abdomen, and pelvis?

GHABACH: [Chest, abdomen, and pelvis imaging] is sufficient unless the patient had any clinical signs that would suggest bone disease.

FINN: I would tend to agree with that; [I would feel] similarly [if the patient had signs that suggested] neurologic disease. It’s very uncommon to see HCC metastasize to the central nervous system, but as patients are living longer, we do sometimes see that.

Do any of you send [for] Foundation Medicine testing on these patients? [Do you use] some other next-generation sequencing?
GHABACH: Not up front, no.

FINN: Yes. Other than, I think, NTRK [translocation], which is a tumor-agnostic indication that occurs very rarely, there’s no biomarker-driven approach for HCC based on the tumor. However, the serum AFP level is linked to the approval of ramucirumab [Cyramza].

FINN: [The disease classification is] stage IV [based on the] T and M components. [According to] the Barcelona system, which is a very common staging system for HCC, this patient would have stage C disease, because they’re well compensated and have extrahepatic spread.

FINN: As mentioned in the National Comprehensive Cancer Network [NCCN] guidelines, the combination of atezolizumab [Tecentriq] plus bevacizumab [Avastin] is [the preferred regimen], supported by level 1 evidence. We published that in the New England Journal of Medicine [in 2020]. This combination showed a marked improvement in survival vs frontline sorafenib [Nexavar].

Sorafenib [had been] the standard of care since 2008. It had been shown to improve survival vs placebo by inducing stable disease [but it did] not have a very high response rate. Since then, no other regimens improved on that until [the advent of] the atezolizumab plus bevacizumab combination. [Sorafenib] was the only approved drug until 2018, when lenvatinib [Lenvima], another recommended regimen, was approved. Yet, lenvatinib was only approved [because it was] noninferior, not superior, to sorafenib in terms of overall survival [OS], though it did have a higher response rate and higher progression-free survival [PFS].

Listed as “useful in certain circumstances,” single-agent nivolumab [Opdivo] currently has no FDA approval. It did have accelerated approval for second-line use, but the phase 3 CheckMate 459 study [NCT02576509] of frontline nivolumab vs sorafenib was negative, so nivolumab lost its approval. I think this NCCN guideline probably came out before that.

Another regimen listed as useful in certain circumstances is FOLFOX, the combination of folinic acid [leucovorin], fluorouracil, and oxaliplatin [Eloxatin]. It is not used in the United States. It has a low level of evidence, [2B]. It is more often used in China where they’ve studied it a little more, but [it] never was shown to be superior to sorafenib in terms of OS.

SNEDDEN: [What would make me hesitant is the patient’s history of] Crohn disease.

FINN: Yes. This patient has Crohn disease, and that’s a relative contraindication to using checkpoint inhibitors. [The patient] is on infliximab as well; you’d have to stop that, presumably. So, [given that] this patient obviously has bad Crohn disease, I would be hesitant to try [the atezolizumab plus bevacizumab combination]. However, I understand the urge to do it, because it’s the most active thing we have; objective response rates were 30%.

The other thing that should give us pause, though, is that the patient also has a history of varices and was banded 2 months ago. Not that that is an absolute contraindication, but in the IMbrave150 study [NCT03434379], all patients [were required] to have had an upper endoscopy within 6 months of coming on study, and they had to have varices treated. [Approximately one-fourth of the patients did have varices, and approximately 10% to 20% had them treated before coming on study.]

So there are 2 contraindications [to using atezolizumab plus bevacizumab]. Lenvatinib [Lenvima] or sorafenib would be very reasonable, and I think it is perceived

DISCUSSION QUESTION
Considering the presence of stage IV disease (classified according to the standards of the American Joint Committee on Cancer), the Child-Pugh score of A, and the history of cirrhosis, what frontline therapy are you most likely to recommend for this patient?

POLLING QUESTION
“What frontline therapy are you most likely to recommend for this patient?”
- Atezolizumab + bevacizumab: 62% (8)
- Lenvatinib: 23% (3)
- Sorafenib: 15% (2)
- FOLFOX: 0% (0)
- Nivolumab: 0% (0)
- Other: 0% (0)

TOTAL VOTES: 13

FOLFOX, oxaliplatin, fluorouracil, and folinic acid (leucovorin).
as being more active because of the high response rate and improvements in PFS. It does have an adverse effect profile that is different from that of sorafenib.\textsuperscript{5,8}

**Polling Question**

“What proportion of your patients with advanced HCC receive tyrosine kinase inhibitor monotherapy as their first-line systemic therapy?”

- 10% 31% (4)
- 11% to 25% 31% (4)
- 26% to 50% 23% (3)
- 51% to 75% 15% (2)
- 75% to 100% 15% (2)

Total Votes: 15

**Discussion Questions**

- Which of the following factors do you consider to be the most important in selecting systemic treatment for this patient: safety and tolerability, response rate, survival, reimbursement, or administration route?
- How would you consider other factors, such as age or sex, in selecting frontline systemic therapy for this patient?

**FINN:** I think, for most of us, patients with advanced HCC are not usually getting tyrosine kinase inhibitor [TKI] monotherapy because presumably there is no contraindication (for atezolizumab plus bevacizumab). I think we would estimate between 10% and 20% of patients have a reason why they can’t get atezolizumab or bevacizumab.

I think contraindications for atezolizumab are probably relatively uncommon; most patients don’t have autoimmune diseases. [Consideration of bevacizumab does raise] a concern about bleeding. However, even though bevacizumab is associated with bleeding, the incidence of very high-grade bleeding events was very uncommon—with a single-digit percentage of grade 4/5 events.\textsuperscript{3}

**GHABACH:** I don’t think that [cirrhosis etiology] is relevant.

**JANA:** [I agree that] it’s not relevant.

**FINN:** I think we do tend to approach the disease like that. There was a paper this year that suggested that [immunotherapy] is not as active in nonviral HCC [as in viral HCC]; however, that has not been proven, per se, in prospective studies.

Are there any toxicities in this patient, or in patients with HCC in general, that concern you?

**GREENBERG:** Yes. In this patient, specifically, I’d be concerned about bleeding. I think it’s safe to use atezolizumab plus bevacizumab, but this patient had varices that were banded, so that would just be something that [would have to be] monitored closely.

**FINN:** I would tend to agree with that if they didn’t have the autoimmune issue. Does it concern you if a patient has untreated hepatitis C or hepatitis B? Or HIV, for that matter?

**GHABACH:** If it’s autoimmune hepatitis, I might think twice about immunotherapy.

**FINN:** Sure, that’s very fair. There are 2 issues, I think, for patients with autoimmune disease. One issue is [that] if they’re on immunosuppression, it’s counterintuitive to use checkpoint inhibitors; it’s like pushing the brakes and the gas at the same time.

The other issue is the challenge of flare. If a patient has psoriasis that is not too disruptive, I give them checkpoint inhibitors without too much concern and if they flare up, I treat them. But something such as autoimmune hepatitis or bad inflammatory bowel disease would have to be [treated more cautiously]. In this case [the patient has had a] prior liver transplant, right? I think that is probably [another] firm contraindication to using checkpoint inhibitors.

How do the Child-Pugh score and liver function [influence your choice of frontline therapy]?

**Snedden:** Well, if the Child-Pugh score were B, then we would use neither the atezolizumab plus bevacizumab combination nor lenvatinib, but rather sorafenib, so it does have an impact on treatment options.
FINN: That brings up an interesting point. The NCCN guidelines initially [listed] even nivolumab [as an option] for [disease with a] Child-Pugh [score of] B, based on a single-arm exploratory study that showed that it was relatively safe. Sorafenib has certainly been around the longest, and there are some safety data [regarding its use in disease with a] Child-Pugh [score of] B.

Survival outcomes are always inferior for patients with a Child-Pugh [score of] B. But we don’t have randomized data that [show whether] that is just the effect of the liver disease or [whether] the drug does improve outcomes for those patients. With the newer drugs such as lenvatinib or, now, atezolizumab plus bevacizumab, I think we need to consider the patients with a Child-Pugh [score of] B as a heterogenous group.

There are some patients who are very functional [in terms of] performance status and symptoms. They have minimal symptoms, they’re up and about, they can come to clinic. For those patients, I don’t have pause about possibly treating them with atezolizumab plus bevacizumab, as long as they don’t have big varices, because I don’t think we add any toxicity with this combination in [patients with a score of] B. Decompensation events are not high risk and, short of autoimmune liver disease, [these patients] should be able to tolerate some [adverse] effects.

The other thing to keep in mind is that some of these patients have Child-Pugh B physiology because they have a very large tumor burden or because they have vascular invasion. If you can induce a response, then their liver disease should get better, and that’s when you need to look at the scans. A patient who has a liver that is coarse on imaging but has a 12- or 15-cm tumor might have some ascites, and maybe their bilirubin would be a little high or their albumin would be low. These are patients who, if you can induce a response, will get better. In that case, atezolizumab plus bevacizumab probably gives them the best chance of a response.

[In contrast], there are some patients who have very shrunken and cirrhotic livers, and the tumor is not that big—perhaps only 5 cm—but the liver is so small [that the tumor] looks giant. In those patients, even if the tumor disappears, they’re still going to be very sick and will probably die around the same time [regardless of treatment], just because they’re decompensated. I think [it is important to remember] that all the phase 3 studies done with any HCC drug are always done in patients who have a Child-Pugh [score of] A.

Does patient preference, or your preference, for an oral regimen vs an intravenous [IV] regimen influence your choice of treatment?

HSU: No, I think only when it comes to [the fact that] some of the drugs may be more expensive.

FINN: So there may be [some influence] on the patient side?

HSU: Yes.

FINN: What about COVID-19? Has that affected your use or management of oral vs IV regimens?

GHABACH: Initially, maybe, a year and a half ago, but not anymore.

FINN: Yes, not anymore. [Keep in mind that] the IV regimen, atezolizumab plus bevacizumab, [requires a visit] once every 3 weeks. But also, because the oral drugs have [adverse] effects, I typically see patients on the oral drugs at least once every 10 to 14 days for the first month or so until we know that the patient is stable. The last thing you want is someone to have diarrhea for 2 weeks and not call or not come in to be seen.

GREENBERG: You mentioned the flare phenomenon. Do you ever, in a patient with an autoimmune condition such as psoriasis, use flare as a surrogate for response?

FINN: No. I don’t think flare or the development of a new autoimmune disease has been correlated with activity of these drugs, or at least with anticancer activity. I think that [is true] across melanoma, lung cancer, all the diseases [in which it has been studied]. Those [adverse] effects seem a little idiosyncratic, and some, such as rash and hypothyroidism, are very common.

CASE UPDATE

The patient began treatment with lenvatinib, 12 mg per day. The patient experienced modest weight loss and reported loss of appetite. This led to a dose reduction to 8 mg per day and a referral for nutritional therapy. At 16 weeks, imaging revealed a partial response. Eight months after initiation of therapy, treatment was discontinued due to disease progression.

DISCUSSION QUESTIONS

• Discuss the selection of lenvatinib for this patient and your own experiences with lenvatinib in this setting.
• What is your experience with adverse effect management with TKIs and, specifically, with lenvatinib?

continued on page 35
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\textsuperscript{1-4}

**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 reinitiating 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.
YOU RESPOND WITH ZEJULA

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS

OVERALL POPULATION (N=733)
- Reduction in the risk of progression or death
- Median PFS: 13.8 months with ZEJULA vs 8.2 months with placebo

HRd POPULATION (n=373)
- Reduction in the risk of progression or death
- Median PFS: 21.9 months with ZEJULA vs 10.4 months with placebo

Study Design: PRIMA, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to first-line platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

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%).

Visit ZEJULAHCP.COM to explore the PRIMA data

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Produced in USA.
5.2 Bone Marrow Suppression

Hematologic adverse reactions, including thrombocytopenia, anemia, and neutropenia, and/or pancytopenia have been reported in patients treated with ZEJULA (see Adverse Reactions [6]). In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 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 QUADO, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 28%, 27%, and 15%, 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 hematologic toxicities do not resolve within 28 days following discontinuation, 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).

6.2 ADVERSE REACTIONS

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

- MDS/AML (see Warnings and Precautions (5.1))
- Bone marrow suppression (see Warnings and Precautions (5.1))
- Hypertension and cardiovascular effects (see Warnings and Precautions (5.1))
- Posterior reversible encephalopathy syndrome (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 most common adverse reactions of all grades in >10% of patients treated with ZEJULA were hypertension (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with 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).

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>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484)</td>
<td>Placebo</td>
<td>ZEJULA</td>
</tr>
<tr>
<td>Placebo (n=244)</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Blood and lymphatic system disorders**

- Thrombocytopenia
- Anemia
- Neutropenia

**Respiratory, thoracic, and mediastinal disorders**

- Hypersensitivity

**Nervous system disorders**

- Insomnia
- Depression
- Nausea

**Musculoskeletal and connective tissue disorders**

- Musculoskeletal pain
- Arthralgia

**Investigations**

- AST/ALT elevation
- Metabolism and nutrition disorders
- Decreased appetite

**Musculoskeletal and connective tissue disorders**

- Musculoskeletal pain

**Nervous system disorders**

- Headache
- Dizziness

**Psychiatric disorders**

- Insomnia

**Renal and urinary disorders**

- Acute kidney injury

**Respiratory, thoracic, and mediastinal disorders**

- Dyspnea
- Cough

**Vascular disorders**

- Hypertension

**Investigations**

- AST/ALT elevation
- Metabolism and nutrition disorders
- Decreased appetite
- Musculoskeletal and connective tissue disorders
- Musculoskeletal pain
Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484) %</td>
<td>Placebo (n=244) %</td>
<td>ZEJULA (n=484) %</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
<td>66</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>74</td>
<td>13</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>71</td>
<td>36</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51</td>
<td>29</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29</td>
<td>17</td>
</tr>
</tbody>
</table>

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 15 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anesthesia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Maintenance Treatment of Recurrent Ovarian Cancer

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 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>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484) %</td>
<td>Placebo (n=244) %</td>
<td>ZEJULA (n=484) %</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>48</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>19</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>21</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Acute kidney injury</td>
<td>21</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>18</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>17</td>
</tr>
</tbody>
</table>

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484) %</td>
<td>Placebo (n=244) %</td>
<td>ZEJULA (n=484) %</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

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 69% 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: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484) %</td>
<td>Placebo (n=244) %</td>
<td>ZEJULA (n=484) %</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
<td>61</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>74</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue/asthenia</td>
<td>57</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>25</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>13</td>
</tr>
<tr>
<td>Investigations</td>
<td>AST/ALT elevation</td>
<td>10</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, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, and epistaxis.

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484) %</td>
<td>Placebo (n=244) %</td>
<td>ZEJULA (n=484) %</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>72</td>
<td>21</td>
</tr>
<tr>
<td>Decrease in white blood cell count</td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td>Decrease in aspartate aminotransferase</td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td>Decrease in alanine aminotransferase</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Decrease in alkaline phosphatase</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%). Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA. Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%). Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.
Thrombocytopenia includes events with preferred terms of aCommon Terminology Criteria for Adverse Events version 4.02. AST/ALT = Aspartate transaminase/alanine aminotransferase.

Sepsis. Neutrophil count decreased, neutropenic infection, and neutropenic:

Skin and Subcutaneous Tissue Disorders: Photosensitivity.

Vascular Disorders: Hypertensive crisis.

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 similar 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. Appraise 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 (12.1) 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 PRIMA, 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 8% 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 (2.3.4 of full prescribing information)]. Nipple reenephalopathy syndrome (PRES).

Psychiatric Disorders: Confusional state/delirium, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).

Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

8.10 Pregnancy

In PRIMA, 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 8% 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.

8.11 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.

8.12 Infertility Males: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (12.1) of full prescribing information].

8.13 Pediatric Use

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

8.14 Geriatric Use

In PRIMA, 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 8% 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.

8.15 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.

8.16 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily [see Dosage and Administration (2.3.4 of full prescribing information)].
There are some patients who are very functional [in terms of] performance status and symptoms. They have minimal symptoms, they’re up and about, they can come to clinic. For those patients, I don’t have pause about possibly treating them with atezolizumab plus bevacizumab, as long as they don’t have big varices, because I don’t think we add any toxicity with this combination in [patients with a score of] B.”

—RICHARD S. FINN, MD

continued from page 29

FINN: In my opinion, the most common challenges with lenvatinib are anorexia, weight loss, and fatigue. Hypertension may occur, but that generally can be managed. This patient had a partial response, and the response rate with lenvatinib [has been shown to be approximately] 19% by RECIST criteria.

DASGUPTA: It’s not a very common disease in my practice, so my range of experience is necessarily limited, but I have found better outcomes with lenvatinib. I’ve not had any problems [with tolerability]. I start at the 8-mg dose, which I’m leery about [increasing] the dose, and I’ve had great responses, but I guess I’ve been lucky. Anorexia [can be a problem so] I use dronabinol, and I’ve not had major problems with weight loss. The hypertension is easily treatable, but sorafenib has been terrible in my hands.

FINN: A friend of mine once said that TKIs [such as lenvatinib and sorafenib] are different from chemotherapy, [in that] if you give someone a taxane, you know what’s going to happen. Everybody gets bone marrow suppression, eventually they’ll get neuropathy, lose their hair, have nausea.

[In contrast,] with the TKIs some patients have no problems and some patients do. I’ve seen a patient get sorafenib and [then require] a wheelchair in a week because they have horrible blisters on their feet. It is very variable.

GUO: My experience [with lenvatinib] is like what you described. Some patients do fine; they’re just fatigued. Normally I would do the same thing—start on 8 mg and try to increase to 12 mg if the patient can tolerate it.

But I’ve also had other patients who are extremely sensitive. I, too, had a patient who developed sores within a week. [Some patients develop] oral mucositis, diarrhea, hand-foot syndrome, hypertension, fatigue, leg swelling, everything. So, yes, it’s variable. I normally start with a lower dosage and see how things go. If the patient can’t tolerate 8 mg, then of course we can’t [increase the dosage], but if they do fine, then I’ll increase the dosage gradually.

FINN: Is there any trick [with managing] fatigue? I struggle with that. [I do discuss] sleep hygiene and check patients’ thyroid-stimulating hormone level. A lot of these TKIs can cause hypothyroidism.⁵

GREENBERG: I often will use low-dose dextroamphetamine while monitoring blood pressure, obviously. You can have a little problem because amphetamines can be appetite suppressants, so [you have to find a good] balance, but I found that 2 mg of dextroamphetamine can give these patients some life. I’ve had more than 1 patient tell me that they have gone dancing for the first time in a long time because it made them feel a little better. [It improves their] quality of life.

FINN: I think most of us are fairly comfortable [with managing the adverse events associated with lenvatinib], using dose reductions and monitoring for [adverse] events.

[In addition to hypothyroidism], proteinuria [is something] you should watch for on a regular basis. Dysphonia
is something that can happen as well, and I don’t think there’s any quick trick. If you do need dose reductions based on weight, [the recommended progression is] 8 mg given daily, then 4 mg daily, and then 4 mg every other day; if you start at the higher dose you have a little more leeway beginning with 12 mg given daily and then following the same progression.

After [our discussion], would [anyone here] change their recommended frontline therapy for this patient?

REDDY: Initially, I [would have chosen] the combination of atezolizumab plus bevacizumab; I’m not convinced [enough] to change my opinion.

FINN: With regard to upfront atezolizumab plus bevaczumab, I think the Crohn disease, controlled with infliximab, would make me [hesitant] to [use that combination]. I think you’d be better off using lenvatinib or sorafenib. Given, diarrhea can happen with these drugs, but it’s by a different mechanism. [Similarly, considering] the gastrointestinal bleeding, I think [both lenvatinib and sorafenib are preferable to atezolizumab plus bevacizumab].

REFERENCES
Targeted Oncology™. In recent years, how have the National Comprehensive Cancer Network (NCCN) recommendations changed regarding first-line systemic therapy for relapsed or stage IV ccRCC? What is currently recommended?

CHAHOUD: Over the past couple of years, these guidelines have changed significantly at multiple levels. The current guidelines make a greater differentiation between patients with favorable-risk and poor-risk or intermediate-risk International Metastatic RCC Database Consortium (IMDC) scores. Our patient falls into the favorable-risk category. In addition to that, 3 approved novel combinations of immunotherapy [IO] plus tyrosine kinase inhibitor [TKI] have been added. These are in addition to the nivolumab [Opdivo] plus ipilimumab [Yervoy] combination [that was approved earlier].

The decision was made to observe the patient, based on the low volume and indolence of the disease and the patient’s preference.

Eighteen months later, the following observations were made:
- Continued indolent growth on scans
- Increased total tumor burden
- A new paratracheal lymph node (measuring 2.0 × 1.5 cm)

These 3 combinations are also listed among the NCCN recommendations for poor-risk and intermediate-risk patients, along with the combination of nivolumab and ipilimumab, all supported by category 1 data. Cabozantinib is also listed as a preferred regimen for patients in this category, probably for patients who cannot tolerate IO due to a history of immune-related disorders or other reasons.

For more case-based articles and videos, scan the QR code or go to TargetedOnc.com/link/1535.
What data led to the approval of the 3 second-line regimens preferred by the NCCN for ccRCC?

The phase 3 CheckMate 025 study [NCT01668784] compared nivolumab with everolimus.\textsuperscript{9} The phase 3 METEOR study [NCT01865747] looked at second-line cabozantinib vs everolimus.\textsuperscript{10} Finally, the phase 2 Study 205 [NCT01136733] looked at lenvatinib plus everolimus vs either lenvatinib or everolimus.\textsuperscript{11} In these trials, patients were TKI-refractory, and the majority had only had 1 prior line of therapy.

The overall response rates [ORR] are important to look at. For nivolumab, the ORR was 25%; for cabozantinib, 17%; and for lenvatinib plus everolimus, 43%.\textsuperscript{9-11} The median progression-free survival [PFS] for nivolumab was 4.6 months, and median overall survival [OS] was 25 months [HR, 0.73; 95% CI, 0.57–0.93; \textit{P} = .002].\textsuperscript{7} That led to the approval of nivolumab for use in the second line in patients who were TKI refractory.\textsuperscript{12} For cabozantinib, the median PFS was 7.4 months [HR, 0.51; 95% CI, 0.41–0.62; \textit{P} < .0001], and the median OS was 21.4 months. A lot of patients had to go through dose reduction with cabozantinib, as we all know.\textsuperscript{10} The starting daily dose of 60 mg is rarely maintained; only around 20% to 30% of patients are able to tolerate cabozantinib at a dose of 60 mg.\textsuperscript{13} Adverse events [AEs] of grade 3 or grade 4 occurred in 71% of the patients who received 60 mg of cabozantinib [daily].\textsuperscript{10} Similarly, AEs of grade 3 or grade 4 occurred in 71% of the patients who received lenvatinib and everolimus; many of these patients [had at least] 1 of the 2 drugs reduced or discontinued.\textsuperscript{11}

For the lenvatinib plus everolimus combination, the OS was in the same range [as those observed for nivolumab and for cabozantinib], and the ORR was a bit higher.\textsuperscript{9-11} These are the data that led to these compounds being the preferred regimens for second-line ccRCC.\textsuperscript{1}

What are the NCCN recommendations for subsequent therapy for ccRCC?

We have a [long] list of options. The preferred regimens for subsequent therapy, supported by category 1 data, are cabozantinib, the combination of lenvatinib plus everolimus—recently added as a preferred regimen—and single-agent nivolumab.

The recommendation of nivolumab was based on some data that do not apply to this patient, and made at a time when frontline IO was nonexistent and our frontline therapy was still sunitinib [Sutent].\textsuperscript{1} Basically, in this patient, the 2 preferred category 1 options for second-line therapy would be either cabozantinib or the combination of lenvatinib and everolimus.

The pembrolizumab plus lenvatinib combination, listed among “other recommended regimens,” was added later for patients who [have been] on frontline nivolumab or frontline nivolumab plus ipilimumab, had some form of response, and later lost that response. [In that case], if the patient is young, has a very good performance status, and does not have any immune-related toxicity, you want to use a tough IO plus TKI combination.

Another recommended regimen, recently added, is tivozanib [Fotivda], a VEGF receptor [VEGFR] inhibitor.\textsuperscript{1,6} This was approved [based on] a phase 3, randomized, open-label, multicenter trial [TIVO-3 [NCT02627963]] that compared tivozanib vs sorafenib in patients who had relapsed or refractory RCC and who had received at least 2 or 3 prior systemic therapies.\textsuperscript{7,8}
During a live virtual event, Chahoud asked participants, “What third-line therapy are you most likely to consider for this patient upon disease progression?”

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivozanib</td>
<td>46% (6)</td>
</tr>
<tr>
<td>Lenvatinib/everolimus</td>
<td>46% (6)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>8% (1)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Other</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

TOTAL VOTES: 13

Please discuss these poll results. Do these answers align with your practice?

Most of us would choose either tivozanib or lenvatinib plus everolimus. I sometimes discuss rechallenging with IO if a patient has had a grade 3 toxicity, but this patient had stable disease and so did not technically respond to the IO plus TKI combination. So, I wouldn’t expect them to respond now. Also, this patient had grade 3 pneumonitis. That worries me; that could have a major impact on the patient’s life and quality of life. It could subsequently necessitate oxygen or an intensive care unit (ICU) admission and could make a patient miserable or shorten his life.

What data are available to guide RCC therapy beyond the second line?

To be honest, we have limited data upon which we can base our choice of third-line therapy.

The data consist mainly of retrospective data and the results of the TIVO-3 study, a phase 3 trial that looked at advanced ccRCC in 350 patients who had progressed on 2 or 3 prior regimens, including at least 1 VEGFR TKI. The patients were stratified according to their prior regimens: a TKI plus a checkpoint inhibitor, 2 TKIs, or a TKI plus something else. The patients were stratified also according to IMDC prognostic score. Patients were randomly assigned 1:1 to receive either tivozanib or sorafenib. At the time of the trial in 2013 and 2014, that was the acceptable comparator in the third-line setting according to the FDA.23 Patients were treated until disease progression. The primary end point was PFS.

The patients were well distributed, and the median age was around 63 years. RCC predominantly affects men, so 70% of the patients were men. The IMDC risk category of most patients was intermediate or poor (about 60% and 20% of patients, respectively). It is interesting that 45% of the patients had been treated with 2 VEGFR TKIs, and 27% had been treated with a TKI plus a checkpoint inhibitor. It’s rare to have data for patients who have been treated previously with a checkpoint inhibitor plus a TKI. Finally, another 28% of the patients had been treated with a VEGFR TKI plus another therapy.

The primary end point was PFS. The trial met its PFS end point [median PFS, 5.6 months vs 3.9 months for the experimental and comparator arms, respectively; HR, 0.73; 95% CI, 0.56–0.94; P = .016]. An important landmark is the 1-year PFS, which was achieved by 28% of patients in the experimental arm and by 11% of patients in the comparator arm. Two-year PFS was achieved by 18% vs 5%, respectively. In a patient who is receiving a third-line therapy, having that disease control for a year is important.

It’s important to highlight that the ORR of tivozanib was 23% [in comparison], even in the second line, the ORR with cabozantinib was 17%; with nivolumab, 25%; and with lenvatinib plus everolimus, 43%. The disease control rate for tivozanib was 82%. The OS end point was not met, but it was trending a bit, getting better with longer follow-up. The median [duration of response] DOR was 20.3 months, with 71% of patients maintaining a response for 1 year, which is more than double [the DOR] observed in the sorafenib arm. So, this regimen provided [many] patients with some good, durable responses.

The safety profile included hypertension; this occurred in a significantly higher number of patients who received tivozanib than in those who received sorafenib. This is to be expected, because tivozanib is specific to VEGFR. Around 27% of patients had hypertension of grade 1 or grade 2, and 20% had hypertension of grade 3. So, you would have to [start] blood pressure management from the beginning, because you know hypertension is going to affect most of your patients.

The diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome [PPE], and rashes were much lower than we [would expect] with a TKI, and that’s because of lesser off-target effects. Only 2% of patients treated with tivozanib had grade 3 or grade 4 diarrhea, vs 10% of those treated with sorafenib. Among patients in the experimental arm, fatigue of grade 3 affected 4%, PPE of grade 3 affected 1%, and grade 3 rash affected none.

The PPE, rash, and nausea and vomiting all affected a smaller percentage of patients in the experimental arm than in the comparator arm. Also, the exposure to drug was nearly twice as long in the experimental arm as in the comparator arm [11.9 months vs 6.7 months, respectively]. Of course, a drug can work only if the patient’s taking it. Finally, dose reduction and dose discontinuation were each required in a smaller percentage of patients in the experimental arm than in those in the comparator arm.

This reflects the greater tolerability of tivozanib than of sorafenib; the longer duration of exposure is important for a third-[line] or fourth-line option.

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How did patients do in the TIVO-3 trial in terms of efficacy and safety?

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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 3.3% of patients treated with ERLEADA® and 2.2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA® and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies. In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and 1% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA®, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event. Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®.

Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

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

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

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

ADVERSE REACTIONS
The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
• Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)
• Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (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.

As soon as you diagnose mCSPC or nmCRPC...
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, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)
TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bicalutamide orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo. Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, mostly 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 to TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthropathya</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rashb</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>Hypertension</td>
<td>18</td>
<td>8</td>
<td>16</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 hyponatremia (3.6% versus 0.6% on placebo).

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>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>Hypertiglyceridemiaa</td>
<td>17</td>
<td>2.5</td>
</tr>
</tbody>
</table>

a Does not reflect fasting values

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

CONTRAINDICATIONS
None.

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

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA and 1% of patients treated with placebo [see Adverse Reactions]. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.2%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

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

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

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 2.7% of patients treated with ERLEADA and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 935 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 1.5%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

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

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

Seizure
Seizures occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and evaluate for loss of activity if medication is recommended when possible or evaluate for loss of activity if medication is continued.

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

Embryo-Fetal Toxicity
The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of apalutamide to pregnant rats during organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose. 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 and Clinical Pharmacology (12.1) in Full Prescribing Information].
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 orchiectomy. The median duration of exposure was 12 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 (12.2%). 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 ≥ 10% on the ERLEADA arm in SPARTAN that occurred with a ≥ 2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥ 15% of patients, and more frequently (≥ 5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

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

a Includes fatigue and asthenia
b Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
c Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
d Includes appetite disorder, decreased appetite, early satiety, and hypophagia
e Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (6% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).

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

| Effect of ERLEADA on Other Drugs | CYP3A4, CYP2C9, CYP19 and UGT Substrates | ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UGT-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

**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 All Grades %</th>
<th>Placebo N=398 N=803 %</th>
<th>Grade 3-4 N=803 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
<td>64</td>
<td>0.5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<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>Hypercholesterolemia</td>
<td>76</td>
<td>0.1</td>
<td>46</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
OVERDOSE
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].
In a patient who is receiving a third-line therapy, having that disease control for a year is important. It’s important to highlight that the ORR of tivozanib was 23%. [In comparison], even in the second line, the ORR with cabozantinib was 17%; with nivolumab, 25%; and with lenvatinib plus everolimus, 43%. The disease control rate for tivozanib was 82.”

—JAD CHAHOUD, MD, MPH

continued from page 39

What is the recommended dose progression for tivozanib?
The starting dose is 1.34 mg, administered orally, over a cycle that consists of 3 weeks on, 1 week off. [If tolerability becomes an issue], medical management of AEs should be attempted before dose interruption or reduction. If necessary, you can reduce the dose to 0.89 mg, administered over a similar cycle—3 weeks on, 1 week off. This drug comes in 1.34-mg and 0.89-mg capsules.6

If a patient treated with a TKI were to develop hypertensive encephalopathy requiring an ICU admission, would you rechallenge that patient with a TKI?
Yes, I would, especially in the case of RCC. If it were a frontline patient, I would probably resume the IO, maximize the benefit from the IO, and then at the time of progression, [rechallenge with the TKI]. Make sure that you’ve taken the time to work closely with the cardiologist to manage the patient’s blood pressure. Make sure that the patient has a [baseline] blood pressure log. [The cardiologist should understand that the patient’s blood pressure] is going to increase by 2 to 4 points, systolic, even when the patient starts in the 110s or 120s, and should have a plan for what to do if [the value] goes to 150 mm Hg.

Whereas, if the patient had [hypertensive encephalopathy] while they were, let’s say, on 2 or 3 blood pressure medications already, then [rechallenging] becomes a bit trickier. I would have a long discussion with the patient about the risks. But if the patient had been on only 1 blood pressure medication, or if the patient hadn’t known that their blood pressure was going up, and now they know and it can be managed, then I would rechallenge. Alternatively, if a patient is doing very well on single-agent IO, you could just try to go as long as you can with the single agent, and you can rechallenge in the future. n

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

Advanced RCC Treatment Selection
Robert Alter, MD, of John Theurer Cancer Center, describes the rationale for treating a 58-year-old man with advanced renal cell carcinoma with the combination of lenvatinib (Lenvima) and everolimus [Afinitor] following progression on first-line therapy.
View more at: TargetedOnc.com/link/1648
SALIT: First I would like to hear from the people who are at transplant centers. What do you use for your standard prophylaxis for transplant in the myeloablative or reduced-intensity setting?

MEI: Historically we use a lot of tacrolimus or sirolimus [Rapamune]. I have used [those] a lot. Part of it is because of how much TBI [total body irradiation] we’ve used, and we still use TBI even for acute myeloid leukemia. So we like tacrolimus or sirolimus because they result in less severe acute GVHD and very rapid [engraftment].

SALIT: So no MMF [mycophenolate mofetil] or methotrexate?

MEI: Over the past couple years, if there was a mismatch, we would just do [posttransplant cyclophosphamide (Cytoxan)]. But historically, we would add low-dose methotrexate if there was a micro mismatch rather than doing ATG [antithymocyte globulin]. But I have been leaning more and more on the posttransplant side. So tacrolimus or sirolimus have just been long-standing [choices].

SALIT: For the risk factors for development of GVHD, there’s donor and recipient factors. The first thing we look at when we look for a donor for patients is whether their human leukocyte antigen [is a] match. We know there’s a 25% chance that the siblings will be a match. Then we do an unrelated donor search through registry to see if there is a donor match. Historically we looked at a 10-out-of-10 match. So we looked at A, B, C, DR, and DQ. And more recently, we’re starting to use DP also as a locus, so a 12-out-of-12 match. In some cases, DP [mismatch] has been shown to confer worse GVHD.

We also look at gender matching, but we look more for male donors even in female recipients because of the donor parody. If you have a donor who has had multiple children, they will have antibodies against the mismatch for that child and that confers a higher risk for GVHD.

Older donor age and CMV-positive donors confer the higher risk of...
GVHD. ABO blood type has been controversial. [Some studies show] it has a higher risk for GVHD if they are mismatched, and some have shown that is not true.

As far as stem cell source, we use almost exclusively peripheral blood. I'm sure you'll see some patients with aplastic anemia that are coming through with bone marrow. At our center, we use probably 80% peripheral blood transplants. There was a study comparing peripheral blood to bone marrow that showed bone marrow had [less risk of] chronic GVHD, which has not translated into clinically using more bone marrow.1 For conditioning intensity, the higher it is, the higher the risk for acute GVHD.

**CASE UPDATE**

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

**SALIT:** For those seeing patients in the clinic after they come back from their transplant, you can look at pictures [showing percentage of involvement] for each arm, leg, and torso. That’s how we calculate the BSA involvement, and [more than] 50% is stage 3. There is also staging of GVHD using episodes and volume of diarrhea per day. The third item [for staging] is the bilirubin from the liver function tests.2

**POLLS QUESTION**

“What would be the priority next step at your institution?”

- Biopsy to confirm GVHD 67% (4)
- Initiate systemic corticosteroid immediately 16% (1)
- Recommend diarrhea treatment and topical steroid for rash 16% (1)
- Test for acute GVHD biomarkers 0% (0)
- Watch and wait 0% (0)
- Other 0% (0)

**DISCUSSION QUESTIONS**

- How do you taper glucocorticoids after achieving initial response?
- Is there a multidisciplinary team–based approach at your center for acute GVHD early recognition and management?

**YAN:** I voted to have a biopsy to confirm GVHD.

**SALIT:** Someone else said recommend diarrhea treatment and topical steroid for rash, and I said start systemic steroid therapy. I think that a couple of things could be true. I think 60% BSA is a lot to treat topically.

**MEI:** What dose of steroids would you do?

**SALIT:** I would probably do 1 mg/kg for this person. I think it’s hard to treat GVHD with less than that. If it’s only the upper GI tract, we sometimes try to do 0.5 mg/kg, but I would do 1 mg/kg for this person. It’s difficult in patients with rashes, especially if they are symptomatic, to wait for biopsy results before treating them.

But I don’t think it’s wrong to do the biopsy. If in your office you can biopsy the skin or have good access to a GI doctor, I think you can biopsy them. I guess then the question is, do you wait for the biopsy to come back before you empirically treat them? I will say probably not if they have 60% BSA area involved. At that point, pull the trigger and start the steroids.

I’m wearing my long-term follow-up clinic hat because I just came out of working at [that] clinic for 1 month. If you have this patient and halfway through the tacrolimus taper, [this happens] and you wonder whether to put the tacrolimus, cyclosporin, or sirolimus back up to therapeutic doses or just start steroids, I usually recommend reinitiating the steroid-sparing agent at the therapeutic dose. I think it cuts back on the duration and the quantity of steroids that you will need.
ARORA: It’s a gradual taper. I think the long-term follow-up care have guidelines of how to taper while monitoring the symptoms.

SALIT: We usually recommend tapering by 10% every 5 to 7 days. So if the patient was started on 1 mg/kg and they successfully resolved, then we would taper by 10%, depending on how early on. If it was acute GVHD, they would be tapered every 3 to 5 days, but if it was delayed acute GVHD, we would usually taper every 5 to 7 days by 10%.

MEI: [At my center], we have a mailing list. For any patient that we suspect has acute GVHD for whom we are considering instituting systemic corticosteroids, their names go on a list that goes to a few of the transplant physicians and the pharmacy team. It’s because we typically have some clinical trial open, like the MAGIC, so we try to get some patients in for trials and talk over their case. In fact, if you don’t email that list and anyone starts systemic steroids, the pharmacist gets notified and then they send an email to the group to discuss what to do next. Some trials you need [to screen patients] within 3 days of steroids, so that’s why we do this—to get patients screened. It’s always Friday afternoon that you can get started on steroids because you need to have something planned for Monday.

SALIT: We do not have anything as coordinated in place. I would say if someone developed acute GVHD, we usually just treat them. The person attending in the long-term follow-up clinic sometimes gets notified if someone starts systemic steroids, the pharmacist gets notified and then they send an email to the group to discuss what to do next. Some trials you need [to screen patients] within 3 days of steroids, so that’s why we do this—to get patients screened. It’s always Friday afternoon that you can get started on steroids because you need to have something planned for Monday.

MEI: When do you consider someone refractory? Is it different if it’s skin vs GI?

SALIT: So that’s a good question. Usually, if they’re 1 week on 2 mg/kg, they’re refractory.

MEI: I was always taught that it takes longer for the GI tract to heal, so you give steroids a little longer, maybe up to 2 weeks. Although usually you see something happening by 1 week. I feel like for skin, there’s a lower threshold to throw in something else. We’ve always tended to give [monoclonal antibodies (mAbs)] relatively early if the rashes are bad stage 3 or 4 skin GVHD, and it’s not turning around within a few days.

SALIT: I did my training at NIH [National Institutes of Health], and we [limited the intake of food]. When I came to [University of Washington], they thought I was crazy because the training now is that, for the patients with GI GVHD, it’s better to feed the gut. So it’s hard to make the diarrhea disappear vs when we used to fast people, and the diarrhea would disappear on that first week on steroids and then we could taper. So I don’t know. I still believe in gut rest, but I think that’s because that was the way I was trained. Gut rest results in less diarrhea and being able to taper the steroids faster.
MEI: This is a fine line. We’ve seen patients with the worst GI GVHD [who] take a pill, and it’s in the stool 30 minutes later. I’ve done a lot of gut rest when it’s bad, and we’ll try to feed them a bland diet when it’s not so bad. But I don’t know where the dividing line is. I’ve probably trained somewhere in the middle in terms of the cultures.

SALIT: Almost everyone said they would reach for ruxolitinib first. Because it’s oral, if patients come with delayed acute GVHD [that] doesn’t respond to steroids, it’s an easy drug to use. I would say, photopheresis, sirolimus, and mAbs are still viable options, [and] in patients that are cytopenic, photopheresis. We still use a lot of photopheresis to be honest, and especially in patients who can’t take oral so it’s hard to give ruxolitinib and sirolimus. ATG, I would say, has completely fallen out of favor in terms of treating acute steroid-refractory GVHD.

The big picture summary [for acute GVHD] is that patients who get high-intensity transplants, mismatched transplants, and peripheral blood transplants are at higher risk. Some things that we’ve done to ameliorate this is using posttransplant cyclophosphamide, ATG, or other T-cell depleting mechanisms.

The concern when you do this is that you have increased [likeliness of] relapse in the patient. So you are always going to have a trade-off between GVHD and relapse. I don’t know if we found anything yet to guarantee that the patient doesn’t get GVHD and doesn’t relapse. We know that there’s some association between GVHD and not relapsing.

We still know steroids are No. 1. I wouldn’t say ruxolitinib has taken the place of steroids [because] we’re not using it as first-line therapy, but we have ruxolitinib as a second-line therapy, which is oral. And other than the cytopenia, [it] is fairly well tolerated.

ARORA: How many patients end up with acute GVHD?

SALIT: At our center, we have about a 60% to 70% rate of acute GVHD. Probably at least two-thirds of them are treated with systemic therapy. So it’s a large percentage.

At other centers, I’ve talked to people at City of Hope, it is quite a bit less. Maybe it’s because we just do a lot of upper GI scoping. So we see a lot of the stage IIA upper GI. We scope people early too. We also do a lot of mismatched transplants at our center still. So a lot of 9/10 matches. We still give a lot of methotrexate and do myeloablative transplants.

I think we do a lot of things that probably cause people to get GVHD. But our relapse rates are very low. So it is a trade-off between GVHD and relapse, but we see a large percentage of patients, more than 50%, with acute GVHD.

ARORA: Does cord blood make a difference?

SALIT: I would say somewhat. But cord blood is going to make more of a difference in the chronic GVHD setting than in the acute setting. We give a lot of high-dose TBI with our cord blood transplants. With kids it’s a little different because they’re getting single-cord transplants. Adults get double-cord transplants, and that confers a higher risk of acute GVHD.

But the cord blood transplants have very low chronic GVHD. With posttransplant cyclophosphamide following peripheral blood transplants, we still see a lot of acute GVHD. So the benefit has been with the chronic, not necessarily the acute. I think ATG is a little different because there is some benefit in acute GVHD as well.

MEI: So a majority of your patients with acute GVHD probably have grade 1 or 2, right? I feel like if they have nausea on day 19 or 20, we’ll usually wait it out. Maybe give them some nonabsorbable steroid and see how it goes.

SALIT: If they’re treated with beclomethasone [Qvar], it is still considered GVHD.

MEI: Sometimes it gets variably recorded as GVHD, and sometimes it doesn’t. So I think there’s some variability there with the data.

SALIT: Yes, it’s difficult. I have a GVHD prevention trial open now, and it’s very complicated. I’ve never had a GVHD prevention trial, and it’s shown me what people call GVHD can be very variable.

MEI: Yes, for sure. We have a [similar] trial in right now.

MITIN: If survival is 1 month for steroid-resistant GVHD, is that the progression-free survival from the disease? What is that 1 month? That is a horrible time frame for the patients with steroid-resistant GVHD.
For appropriate patients faced with relapsed/refractory multiple myeloma

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**

**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 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 21% 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 14%. 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 before 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 was observed in dose reduction, 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.

Advises 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 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 (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 x ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

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Produced in USA.

**BLENREP belantamab mafodotin-blmf for injection 100 mg**

Made for this Moment
BLENREP (belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product 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 [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 ophthalmic 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% 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, 9% were in follow-up, and 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 machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].

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:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- 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.BLENPREMRM.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 29%, 23%, and 17% 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]. Administer predmedication 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:

- Ocular toxicity [see Warnings and Precautions (5.1)].
- Thrombocytopenia [see Warnings and Precautions (5.3)].
- 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 observed 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 = 95). 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 adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (25%) and thrombocytopenia (5%).

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 2 summarizes the laboratory abnormalities in DREAMM-2.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLNREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Keratopathy^</td>
<td>71 (44)</td>
</tr>
<tr>
<td>Decreased visual acuity^</td>
<td>53 (28)</td>
</tr>
<tr>
<td>Blurred vision^</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Dry eyes^</td>
<td>14 (1)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (1)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (2)</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions^</td>
<td>21 (3)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (2)</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12 (0)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection^</td>
<td>11 (0)</td>
</tr>
</tbody>
</table>

^ Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

^ Visual acuity changes were determined upon eye examination.

^ Decreased visual acuity included diplopia, vision blurred, visual acuity reduced, and visual impairment.

^ Dry eyes included dry eye, ocular discomfort, and eye pruritus.

^ Fatigue included fatigue and asthenia.

^ Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, tachycardia, and tachycardia.

^ Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

**Eye Disorders:** Photophobia, eye irritation, infective keratitis, ulcerative keratitis.

**Gastrointestinal Disorders:** Vomiting.

**Infections:** Pneumonia.

**Investigations:** Albuminuria.

### Table 2. Laboratory Abnormalities (>20%) Worsening from Baseline in Patients Who Received BLNREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLNREP N = 95</th>
</tr>
</thead>
<tbody>
<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, ≥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 toxin 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-blmf 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 (8.2)].

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 or older, 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 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 75 years and 75% of patients aged 75 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 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].

Infertility

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

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For:

GlaxoSmithKline
Research Triangle Park, NC 27709
©2020 GSK group of companies or its licensor.
August 2020 BRP:1BRS
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BLMADVT190001 January 2021
Produced in USA.
SALIT: Steroid-resistant GVHD has a terrible prognosis. Twenty percent have a 6-month survival. So [for the phase 3 REACH2 trial (NCT02913261), the median failure-free survival was 1 month for the control arm vs 5 months for the ruxolitinib arm].

I guess it’s not necessarily that they only survived 5 months vs 1 month, but it’s unclear to me if the failure was death or just progression and they were treated with something else. I don’t know. I agree with you. It’s confusing because this is failure-free survival.

MITIN: Are they talking about the initial disease during the steroid-resistant phase?

SALIT: Yes, once there is steroid-refractory or steroid-dependent GVHD and they start ruxolitinib or best-available therapy. How long did they live for? I don’t know. This is confusing because it’s treatment failure. But then it’s unclear if they failed that treatment, did they go onto [another] treatment? Maybe they did and survived. I don’t know. But yes, I think the 5 months vs 1 month is the failure-free survival. I would say third-line therapy is even more unsuccessful than second-line therapy.

REFERENCES
**BREAST CANCER**

**Roundtable Discussion: Isaacs Discusses Second- and Third-Line Therapy for Patients with TNBC**

**CASE SUMMARY**

A 48-year-old woman with T1N1 triple-negative breast cancer (TNBC) received adjuvant dose-dense doxorubicin and cyclophosphamide-paclitaxel, which she tolerated well. Laboratory results showed both her alanine aminotransferase and aspartate aminotransferase levels were 1.5 times the upper limit of normal. CT scans showed 1 liver and 2 left lung lesions, and the biopsy of the liver lesion confirmed recurrent metastatic TNBC, but her brain MRI was negative for brain metastasis and genetic panel testing was also negative. Central pain syndrome was 0%, there were no significant comorbidities, and the patient had an ECOG performance score of 0. Eight months after completion of adjuvant therapy the patient reported worsening fatigue, and she received frontline gemcitabine and carboplatin with a documented partial response lasting 6 months. After that treatment, she reported worsening fatigue and new disease progression was discovered and she now has an ECOG score of 1.

**DISCUSSION QUESTION**

- What do you recommend as second-line therapy for this patient’s metastatic TNBC?
- What are the therapeutic options for this patient with rapid recurrence?
- Which would you seriously consider?
- Which one are you most likely to recommend and why?
- If you chose chemotherapy or other in the polling question, what agent/regimen are you most likely to recommend?
- What do you consider the ideal therapeutic sequence for PD-L1-negative, BRCA-negative metastatic TNBC?

**GORBATY:** I would strongly consider sacituzumab [Trodelvy], because [the patient is failing treatment] in less than 12 months from active chemotherapy.

**ISAACS:** What do others feel?

**KATRAGADDA:** I agree with sacituzumab in this setting, as she had early progression within less than 12 months, and she qualifies for its labeled indication.

**SMITH:** [In my opinion], unfortunately, this patient is not curable. I think sacituzumab is still [the correct choice to me] and she has got a good performance status. Capecitabine is also a great drug choice.

**HAGAN:** I love the idea of capecitabine, but I’m also thinking this patient might do potentially better with eribulin [Halaven], because that in a clinical trial, I thought, performed better than capecitabine. I could potentially use capecitabine at a time when the patient is a little bit more beat up and looking for something that was a little easier to go with, but I totally love the
idea of capecitabine. I’d have to have a good conversation with the patient that that might not, survival-wise, be the best bet, potentially.

GORBATY: What do you think the response rate to capecitabine in this setting would be?

ISAACS: This is a patient who obviously has a very poor prognosis, and who relapses so quickly after dose-dense [chemotherapy treatment]. I think it is unlikely that she would have a response, but the issue with what we do is that we don’t have good markers of who is going to respond to which therapy, and I think we all recognize that that’s where we’re trying to get to. However, I think she probably has a small chance of responding to capecitabine, but I understand the rationale that people are using for this, and sacituzumab is currently approved after 2 prior lines of chemotherapy, including 1 in the adjuvant setting.2

I think we’ve all had experiences where we might have requested that drug and been unable to get it. I think that there were some good points brought up about eribulin, but the question now is how we would sequence things, and I think one of the things that I always think of with our metastatic patients is we need to think about sequencing, but we’re typically not. But I think people had a good rationale for the various approaches. I think that personally, I would have tried to put her on a clinical trial, because obviously, she doesn’t have very chemo-sensitive disease. We recognize that we don’t have trials available for these people, so we don’t always have that as an option, but in terms of other things, I probably would have leaned more toward sacituzumab or eribulin, but I think capecitabine is a very reasonable choice in her as well.

SMITH: Well, I didn’t choose that, but the immediate thing is to try to grab for a platinum therapy, right? So carboplatin [in my opinion].

ISAACS: We didn’t have a chance to talk about that there, but the concept, you’re using carboplatin for TNBC.

SMITH: Or that in fact that she did have paclitaxel, and try to use nanoparticle paclitaxel.

ISAACS: What would your front-line treatment have been between 8 months and 24 months for relapse?

SUDARSAN: I would probably be keener to use chemotherapy here on a patient that had that 2-year gap between her adjuvant therapy and a relapse. I would probably go toward something like eribulin.

WENG: It depends on [the patient’s] goals, and it sounds like she’s active, good performance status, young, and probably, I presume, wants to be very active, so oftentimes, for those patients, I go with oral capecitabine to give them the most latitude for their activities, and to be able to titrate the tolerability. I do restage relatively soon after starting, just to make sure I’m on the right track, because my other go-to for single agent is eribulin. I’ve had a good experience with that, but it does tie patients up, and does have greater intolerability compared with capecitabine.

ISAACS: So let’s think about the patient with rapid recurrence, and the question about why you made these decisions and at this point, [have chosen sacituzumab govitecan]. What is it that’s guiding this recommendation for you?

BHANDARI: [The patient in this case] has progressed quite oddly after the initial therapy of 8 months. She has, I would say, an overall poor prognosis. If the clinical trial is not available, I think I will probably go with a combination of carboplatin/gemcitabine, because she had not received carboplatin/platinum and Gemzar, so that would be

**POLLLING QUESTION**

“If this patient had metastatic recurrence 24 months after adjuvant therapy, what would you recommend as second-line therapy for this patient’s metastatic TNBC?”

- Sacituzumab govitecan 50% (5)
- Antimetabolite (capecitabine) 20% (2)
- Platinum agent 20% (2)
- Microtubule inhibitor (eribulin, vinorelbine) 10% (1)
- Anthracycline 0% (0)
- Clinical trial/other 0% (0)

TOTAL VOTES: 10

ISAACS: For those of you who chose combination chemotherapy, what were you thinking of in this patient? And let’s turn it back to [when] after 8 months, she progressed, as opposed to now. What combinations are people thinking about?
You can have very motivated patients who want to have the most aggressive chemotherapy approach, because not only do they have large disease burden, but they do feel that they want to be as aggressive as possible. So that gives you that option, but there are other patients who don’t want as much toxicity, so more customized chemotherapy gives them more flexibility for their lifestyle, and if they haven’t had capecitabine before, then that’s an option.”

—DAVID WENG, MD

ISAACS: Does anybody else have thoughts or comments about that, or how they made their choice here?

HAGAN: I picked sacituzumab in this situation because my memory of the clinical trial was that sacituzumab was being compared with physician’s choice of single-agent chemotherapy and won out on both progression-free survival [PFS] and overall survival [OS], so we do have a little bit of a hint as to, at least for single-agent chemotherapy, sacituzumab beat out what the physicians chose. I mean, that’s kind of a real-world study in some ways. Use your best option if you don’t choose sacituzumab, and there was an OS advantage of something like 12 months vs about 7 months. I don’t know how many people in the physician’s choice arm then might have been able to go on to get sacituzumab second line, further line, so it was a question of early vs late, but at least we do have a hint, if you didn’t have that option, that sacituzumab was going to win out. So again, what I would have done otherwise, which again, probably would have been eribulin.

ISAACS: I know there has just been a rush of different drugs out there, and lots of different trials, but there is the ASCENT trial [NCT02574455] that did look at that and found what you said, and my guess is that most patients didn’t go on to get sacituzumab, because it wasn’t available. These patients tend to progress quite quickly, so it’s fairly unlikely that they did, although some might have gotten it subsequently after its approval.
Do people want to talk about what they think is the ideal sequence of drugs for a patient who [we have stratified based] on their PD-L1 status? We have one sort of algorithm that we go down if they are PD-L1 positive, and a different one if they are PD-L1 negative. So for PD-L1-negative [patients in the first line] it sounded like people are using a variety of different choices, including eribulin, capecitabine, some carboplatin, and then in the second line, it looked like, from the poll, that many people were choosing sacituzumab. However, for a patient who had had disease progression, her original disease-free interval was longer and there was more variability. Do people have a set algorithm [to look at their PD-L1 status]?

**GAI:** It’s quite individualized to me, for example, if somebody has a large tumor burden, I’d probably try the doublet like you did, carboplatin, the gemcitabine, first-time palliative chemotherapy. After that, I’m not sure the doublet is going to offer any benefits. I will try the single agent, but if the patient has a quick progressive disease, I will probably avoid the capecitabine or the pill form. I’d try the IV drug, and I’d try to switch to sort of a fundamentally different mechanism of action, like sacituzumab, rather than something else. That’s my sort of philosophy.

**ISAACS:** Does anyone feel differently? Is there any place where you would all put 1 drug? Like, there’s variability, but is your second-line choice always this, or is there anything, or most often, there’s never always in medicine, and I always tell the medical students and residents that there’s no always and nevers in medicine. However, your general go-to in the first line or second line or third line, but variability in some of the other lines, anything that people are thinking about that, and what drives that choice, if that’s what they’re doing?

**WENG:** One of the items is, as somebody mentioned, the disease burden and how aggressive the patient wants to be. I think that the carboplatin/gemcitabine combo is very active, and it does have a higher response rate in my experience, but also more toxicity. You can have very motivated patients who want to have the most aggressive chemotherapy approach, because not only do they have large disease burden, but they do feel that they want to be as aggressive as possible. So that gives you that option, but there are other patients who don’t want as much toxicity, so more customized chemotherapy gives them more flexibility for their lifestyle, and if they haven’t had capecitabine before, then that’s an option.

There are a lot of triple-negatives who get capecitabine because they got neoadjuvant therapy and then had a partial response, so it’s always a matter of, I think, disease burden is a factor, too, to choosing therapy, and that’s always a consideration.

**DISCUSSION QUESTION**

- How do you feel about the FDA approval?
- How do you interpret it?
- Was it something you were happy about? Did you feel that it offered your patients some new options?

**GORBATY:** I was happy about it. I think the earlier you use it, it gives more patients an opportunity to benefit from it, and I think it may eventually be a first-line option, though it isn’t currently approved for that. So I was wondering, do we know what the response rate or PFS is when you use it first line vs second vs third?

**ISAACS:** I think maybe we’ll get some forest plots coming along that will show, I think, one of the breakdowns, so we can look at that in a second. But if I’m interpreting right, Mayer, what you were also interested in, or what was good about this, was that it was approved earlier on than the conditional approval. It allowed you to give it after just 1 line of therapy, and that was something that you found appealing. Is that right?

**GORBATY:** I mean, we all know that with each line of therapy, people fall off, and they never get a chance to be exposed to a drug, so the earlier you can give it, potentially the more people can benefit.

**KATRAGADDA:** It opens more opportunities for the patients to receive this if it is approved in the first-line metastatic setting....I thought it was...he could use it in the first line, if you had progressed within 6 months to a year after adjuvant, that could be counted as 1 line of treatment, but as the previous colleague has mentioned, of patients from each line of treatment, so the sooner you get it the better it is, given that it has beaten out the standard of care or physician’s choice treatments.

**REFERENCES**

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

Consistent results with or without prior adjuvant chemotherapy

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

*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.

†Control arm=placebo.

‡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).

CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; HR, hazard ratio; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

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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† Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases.

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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.

OVERWHELMING EFFICACY

ADJUVANT TAGRISSO: DELIVERING THE FIRST EVER TARGETED THERAPY in resected EGFRm NSCLC patients

TAGRISSO demonstrated extraordinary disease-free survival (DFS) Probability in resected EGFRm NSCLC patients.

DFS Probability

<table>
<thead>
<tr>
<th>Months</th>
<th>2-year DFS rate</th>
<th>1-year DFS rate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>44%</td>
<td>90%</td>
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</table>

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

1 ORAL TAGRISSO FOR 3 YEARS or until disease recurrence/unacceptable toxicity.1,2,4

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.1,2,4

SELECT SAFETY INFORMATION

- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a QTc >500 msec, and 3.1% of patients had an increase from baseline QTc >60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia

- Cardiomyopathy 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% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <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 symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO.

- 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.

- 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.

- Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and IgA 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.

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

- Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough.

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>Interstitial lung disease (ILD)/Pneumonitis</td>
<td></td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>Cardiac (see Warnings and Precautions (5.2, 5.3) in the full Prescribing Information)</td>
<td></td>
<td></td>
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<tr>
<td>QTc interval greater than 500 msec on at least 2 separate ECGs</td>
<td>Withhold TAGRISSO until QTc interval is less than 500 msec.</td>
<td></td>
</tr>
<tr>
<td>QTc interval prolongation with signs/symptoms of life-threatening arrhythmia</td>
<td>Permanently discontinue TAGRISSO.</td>
<td></td>
</tr>
<tr>
<td>Symptomatic congestive heart failure</td>
<td>Permanently discontinue TAGRISSO.</td>
<td></td>
</tr>
<tr>
<td>Cutaneous (see Warnings and Precautions (5.5) in the full Prescribing Information)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome (SJS), Erythema Multiforme Major (EMM)</td>
<td>Withhold TAGRISSO if suspected and permanently discontinue if confirmed.</td>
<td></td>
</tr>
<tr>
<td>Other (see Adverse Reactions (6.1) in the full Prescribing Information)</td>
<td></td>
<td></td>
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<tr>
<td>If improvement to Grade 0-2 within 3 weeks</td>
<td>Resume at 80 mg or 40 mg daily.</td>
<td></td>
</tr>
<tr>
<td>If no improvement within 3 weeks</td>
<td>Permanently discontinue TAGRISSO.</td>
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</table>

* Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).

† QTc = Interval corrected for heart rate

‡ ECGs = Electrocardiogram

Drug Interactions

Strong CYP3A4 inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A4 inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer [see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information].

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease/Pneumonitis

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 with 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].

QTc Interval Prolongation

Heart rate-corrected (QTc) QTc interval prolongation occurs in patients treated with TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 0.8% were found to have a QTc > 500 msec, and 3.1% of patients had an increase from baseline QTc > 500 msec [see Clinical Pharmacology (12.2) in the full Prescribing Information]. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QT interval. If a QTc prolongation is observed, discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia [see Dosage and Administration (2.4) in the full Prescribing Information].

Cardiomyopathy

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 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (9/525) of patients treated with TAGRISSO experienced a 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 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 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 IgA vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if cutaneous vasculitides 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.

Embryo-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 exposure 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 of reproductive potential prior to initiating TAGRISSO. 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 of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to 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)] and two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=175) [see Warnings and Precautions (5)] in the full Prescribing Information]. Of these patients, 1479 patients who received TAGRISSO, 81% were exposed for 6 months or longer and 66% were exposed for greater than one year. In this pooled safety population, the most common adverse reactions in ≥ 10% of 1479 patients who received TAGRISSO were diarrhea (47%), rash (45%), mucositis (44%), fatigue (33%), nausea (32%), constipation (26%), fatigue (21%), and cough (20%). The most common laboratory abnormalities in ≥ 20% of 1479 patients who received TAGRISSO were leukopenia (65%), lymphopenia (62%), thrombocytopenia (53%), anemia (47%), and neutropenia (33%).

The data described below reflect exposure to TAGRISSO (80 mg daily) in 337 patients with EGFR mutation-positive resectable NSCLC and 558 patients with EGFR mutation-positive metastatic NSCLC in three randomized, controlled trials [AURA (n=337), FLAURA (n=279), and AURA3 (n=279)]. Patients with a history of intercurrent radiation exposure, chronic asthma, and chronic obstructive pulmonary disease were excluded from enrollment in these studies.
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 dose reductions or interruptions were diarrhoea (4.5%), stomatitis (3.9%), nail toxicity (1.8%) and rash (1.8%). Adverse reactions leading to permanent discontinuation occurred in 11% of patients treated with TAGRISSO.

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

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 TAGRISSO in ADAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=337)</th>
<th>Placebo (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>47 (14)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32 (9)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>12 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>40 (12)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>37 (11)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>29 (9)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 (6)</td>
<td>9 (3)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19 (6)</td>
<td>19 (6)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (5)</td>
<td>25 (7)</td>
</tr>
<tr>
<td><strong>Infection and Infestation Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (4)</td>
<td>9 (3)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (3)</td>
<td>9 (3)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (4)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (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</td>
<td>54 (16)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>47 (14)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>44 (13)</td>
<td>14 (4)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25 (7)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>24 (7)</td>
<td>14 (4)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (3)</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (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>Diarrhoea</td>
<td>58 (21)</td>
<td>57 (21)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32 (12)</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (5)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (5)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>58 (21)</td>
<td>71 (26)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>36 (13)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>35 (13)</td>
<td>53 (19)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17 (6)</td>
<td>14 (7)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (8)</td>
<td>14 (5)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20 (7)</td>
<td>25 (9)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (6)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13 (4)</td>
<td>7 (4)</td>
</tr>
</tbody>
</table>

### Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA (cont’d)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 (23)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>Anemia</td>
<td>59 (21)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>51 (19)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41 (15)</td>
<td>10 (4)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>20 (7)</td>
<td>29 (10)</td>
</tr>
</tbody>
</table>

### Table 5. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 (23)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>Anemia</td>
<td>59 (21)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>51 (19)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41 (15)</td>
<td>10 (4)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>20 (7)</td>
<td>29 (10)</td>
</tr>
</tbody>
</table>
chemistry-treated patients. The trial population characteristics were: median age 62 years, aged less than 65 (35%), aged 65, 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 chemotherapy 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 (LLD/pancreatitis).

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%).

Tables 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3. Adverse reactions occurring in >10% of patients receiving TAGRISSO in AURA3.*

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
<td>All Grades (%)</td>
</tr>
<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>5.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11.0</td>
<td>2.2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Grade 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia§</td>
<td>27.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Hypotremia‡</td>
<td>26.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Hyperkalemia§</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Hypokalemia§</td>
<td>9.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

### 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- and 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 corresponding BCRP or P-gp substrate (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 the drug is administered concomitantly with TAGRISSO.

**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.

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 implantation through the closure of the hard palate (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 control litters. 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].

**Males**

Advise male patients with female partners 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].

**Females**

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO 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**

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

**Geriatric Use**

Forty-three percent (43%) of the 1479 patients in ADAYA (n=1,573), FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=2,10), and AURA1 (n=1,73) 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 (Child-Pugh C or total bilirubin > 3 to 10 times ULN and any AST) [see Clinical Pharmacology (12.3) in the full Prescribing Information].

**Distribution**

AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

TAGRISSO® (osimertinib) tablets, for oral use
Targeted Oncology™: What phase 3 trials have addressed first-line maintenance after platinum-based therapy for patients with advanced ovarian cancer?

CRANE: The GOG-0218 trial [NCT00262847] examined maintenance with bevacizumab [Avastin] plus carboplatin and paclitaxel vs maintenance with carboplatin and paclitaxel alone. We can’t talk about maintenance therapy and ignore this trial. In this trial, the key patient population was all comers, and they were treated for 15 months with bevacizumab maintenance. There was about a 3-month improvement in progression-free survival [PFS].

The duration of bevacizumab maintenance in [the GOG-0218] trial is the duration that, as physicians, we generally use, and this [serves as] important background for some of the other trials, specifically PAOLA-1 [NCT02477644].

There are 3 trials that looked at maintenance with PARP-targeted therapies: SOLO-1 [NCT01844986], PRIMA [NCT02655016], and PAOLA-1. These phase 3 trials had different patient populations and different study drugs.

The SOLO-1 trial compared olaparib [Lynparza] with placebo in the frontline maintenance setting after chemotherapy. In this trial, patients had to have a germline or somatic BRCA mutation and high-grade serous or endometrioid adenocarcinoma. Patients had [previously achieved] a complete or partial response to first-line platinum therapy and in this trial were randomized in a 2:1 fashion to receive either olaparib at 300 mg twice a day or placebo. Duration of treatment with olaparib was 25 months, or about 2 years. The primary end point was investigator-assessed PFS. The FDA’s first-line maintenance indication [for this drug] is not all comers, because the trial only looked at patients with either germline or somatic tumor BRCA mutations.

The PRIMA trial looked at niraparib [Zejula] maintenance in the first-line setting. This study had a slightly more unfavorable population, with patients at high risk for progressive disease with stage III or IV cancer. This study included all comers, so patients did not have to have a BRCA mutation, [though] the study did look at homologous recombination deficiency [HRD]. These patients [were required to have had] either a complete or partial response to first-line platinum treatment. The patients were stratified according to whether they had received neoadjuvant chemotherapy, the type of pelvic nodules for stage IIIIC high-grade serous ovarian cancer

- No gross residual disease
- Germline molecular testing: BRCA wild-type; homologous repair deficient
- She was treated with intravenous carboplatin and paclitaxel with NK1, 5HT3, and dexamethasone but experienced chemotherapy-induced nausea and vomiting prophylaxis.
  - She experienced persistent daily nausea with vomiting on day 1 after chemotherapy.
- After completion of chemotherapy, CA 125 was 14.2 U/mL; clinically no evidence of disease
  - Patient reports continuing daily nausea.

Erin Crane, MD, MPH
Gynecologic Oncologist
Atrium Health Levine Cancer Institute
Charlotte, NC

March 2013

- A 49-year-old Black woman presented to her primary care physician with complaints of abdominal bloating and nausea.
- Medical history: chronic hepatitis B virus; mild hypertension
- Family history: The patient’s mother died of breast cancer at aged 59 years; a cousin on her mother’s side died of ovarian cancer at age 65 years.
- CT scan: ascites and bilateral 8-cm adnexal masses
- Cancer antigen (CA) 125: 285 U/mL
- She underwent exploratory laparotomy followed by omentectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, appendectomy, and resection

PRIMA [NCT02655016], and PAOLA-1 have been pivotal in advancing the field of maintenance therapy in ovarian cancer.
of response they had to chemotherapy, complete or partial, and whether they were positive or negative for HRD. Patients were randomized in a 2:1 fashion to receive niraparib [300 mg once a day] or placebo. Patients were treated until disease progression or to 3 years—a longer duration of treatment. The primary end point was PFS.\(^7\)

The PAOLA-1 trial was conducted with patients who had completed first-line platinum-based chemotherapy.\(^{10,11}\) Again, the key patient population was all comers; patients didn’t have to have BRCA mutations or HRD. Patients were randomly assigned to receive maintenance either with bevacizumab plus olaparib or with bevacizumab plus placebo.

The duration of treatment was 15 months for bevacizumab and 24 months for olaparib.\(^4\) Some of us have raised issues with this trial because there was no olaparib-only arm, but it is an interesting study. Both PAOLA-1 and PRIMA resulted in FDA approval for patients who have had a complete or partial response to first-line platinum-based treatment.\(^{12,13}\) In the case of PAOLA-1, approval was for patients who are HRD positive or who have genomic instability.\(^12\)

**In those trials, how did patients in the overall population fare with respect to PFS?**

In the SOLO-1 trial, there was an astronomical difference in PFS between patients who received olaparib vs those who received placebo [56.0 months vs 13.8 months, respectively; HR, 0.33; 95% CI, 0.25-0.43].\(^5,14\) Keep in mind that these were all patients who had BRCA mutations, so we know that these patients are going to have a better overall prognosis and response to treatment.

In the PRIMA trial, there was about a 5-month improvement in PFS among all comers who received niraparib compared with those who received placebo, 13.8 months vs 8.2 months, respectively [HR, 0.62; 95% CI, 0.50-0.76; \(P<.001\)]. But among patients with BRCA mutations, there was an increased magnitude of improvement: 21.9 months vs 10.4 months, respectively [HR, 0.43; 95% CI, 0.31-0.59].\(^7\)

In the PAOLA-1 trial, PFS was 22.1 months among all comers who received bevacizumab plus olaparib vs 16.6 months among those who received bevacizumab plus placebo [HR, 0.59; 95% CI, 0.49-0.72], an improvement of about 6 months.\(^4\)

The National Comprehensive Care Network [NCCN] guidelines now incorporate all these trials into their recommendations.\(^15\)

**Can you elaborate on the results of the SOLO-1 trial of olaparib?**

When these results were first presented, there were gasps in the audience. We started to think, “Hey, maybe we’re actually curing patients of their cancer.” At 24 months, the Kaplan-Meier curves are separated; this is the 2-year mark at which we say, “Well, maybe this [cancer] isn’t coming back.” In continuation up to 60 months, the curves remain separated.\(^14\) There was an incredible HR as well; we almost never see that for ovarian cancer.

When we do these trials, we try to determine whether any particular subgroup benefited more or less than others. This study’s subgroup analysis showed that all patients benefited [from olaparib treatment]. This was true regardless of the patients’ BRCA1 and BRCA2 mutation status, their disease stage, and their response to chemotherapy—complete or partial.\(^5\)

The main adverse events [AEs] were cytopenias: thrombocytopenia, anemia, and neutropenia. There were some other AEs, like nausea, fatigue, and constipation. It’s important to note that a [meaningful] proportion of patients in the placebo group had AEs as well. We have to remember that these patients had received 6 cycles of chemotherapy, and many of them were still tired and nauseated from that treatment.\(^5,14\) That does [affect patients who are] started on PARP maintenance.

The ASCO guidelines have a lot of information. Basically, we know that anyone who has epithelial ovarian, fallopian tube, or primary peritoneal carcinoma should be offered germline BRCA1 and BRCA2 testing and even expanded panel testing.”

—ERIN CRANE, MD, MPH
What other details can you share about the PRIMA trial of niraparib?
In this trial, a large proportion of patients [about a third] had stage IV disease, and a large proportion—over half—had received neoadjuvant chemotherapy. This more unfavorable population really [precludes] cross-trial comparisons [with SOLO-1 and PAOLA-1].

The subgroup analysis was interesting. It’s important to remember that the FDA has approved niraparib maintenance for anyone who has had a complete or partial response after first-line therapy, regardless of HRD status. In patients who had 

BRCA mutations and had HRD, there was a median PFS of 22.1 months in the experimental arm and 10.09 months in the control arm [HR, 0.40; 95% CI, 0.27-0.62; \( P < .001 \)]. As you would expect, this subgroup experienced the largest magnitude of benefit in response to niraparib treatment.

Patients who did not have germline 

BRCA mutations but who did have HRD, the inherited somatic defect in DNA repair, still experienced a large magnitude of benefit: 19.6 months in the experimental arm vs 8.2 months in the placebo arm [HR, 0.50; 95% CI, 0.31-0.83; \( P = .006 \)]. [In contrast], patients who were negative for HRD experienced a benefit of much smaller magnitude: 8.1 months in the experimental arm vs 5.4 months in the control arm [HR, 0.68; 95% CI, 0.49-0.94; \( P = .020 \)]. This result [prompted discussion about whether we should] offer somatic testing to all patients or offer niraparib maintenance to all patients regardless of HRD status.

Subgroup analysis revealed that pretty much all comers experienced some magnitude of benefit favoring niraparib over placebo. This included subgroups defined by disease stage and defined by whether patients had received neoadjuvant chemotherapy.

Interim analysis of overall survival [suggests that] niraparib is favored over placebo, but the overall survival event rates are low. In other words, there haven’t been that many deaths yet, so we can’t draw any definitive conclusions; that will be presented at a future meeting.

Treatment-related AEs were manageable and consistent with the PARP inhibitor class. As expected, a higher proportion of patients on treatment than of those on placebo experienced thrombocytopenia, anemia, neutropenia, nausea, fatigue, and constipation. But similar to what was observed in the SOLO-1 trial, a [meaningful] proportion of patients who received placebo after completing chemotherapy were tired after that treatment and had some AEs. [For example], 1 patient had myelodysplastic syndrome after 9 months of niraparib treatment. That is why we continue to monitor these patients very closely.

Can you discuss more about the results of the PAOLA-1 trial of bevacizumab plus olaparib?
In this study, the percentage of patients exhibiting PFS at 12 months, at 18 months, and at 24 months was consistently greater in the bevacizumab plus olaparib group than in the control group, [at 24 months, 46% vs 28%, respectively].

There was a greater magnitude of benefit observed among patients who had 

BRCA mutations [in the experimental and control arms, 37.2 months vs 17.7 months, respectively; HR, 0.33; 95% CI, 0.25-0.45]. Among patients who did not have 

BRCA mutations but who were HRD positive, PFS was 28.1 months vs 16.6 months, respectively [HR, 0.43; 95% CI, 0.28-0.66]. Patients who did not have 

BRCA mutations and who were HRD negative did not have as much benefit, only 16.6 months vs 16.0 months, respectively [HR, 0.92; 95% CI, 0.72-1.17].

There weren’t any surprises in terms of AEs. The AEs included some hypertension and proteinuria, which are associated with bevacizumab, and cytopenias caused by olaparib.

What dosage guidance exists for physicians using niraparib or olaparib?
During an interim analysis in the PRIMA study of niraparib, it was noted that patients with a body weight less than 77 kg or with a starting platelet count less than 150,000/\( \mu L \) often required a dose reduction or interruption. So about halfway through the study, the dosing was changed so that such patients started on a once-daily dose of 200 mg. I’ve had to dose reduce, and patients worry that it’s less effective. However, an exploratory analysis suggested that there was still a significant PFS benefit to HRD-positive patients [HR, 0.39; 95% CI, 0.22-0.72] and to the overall patient population [HR, 0.68; 95% CI, 0.48-0.97]. It is recommended to start niraparib maintenance no later than 12 weeks after completion of the most recent platinum-containing regimen, which is plenty of time.

I would say that if a patient hasn’t recovered from their hematologic toxicities, or other toxicities, at the 3-month mark, then they’re probably not the best candidate for PARP maintenance anyway.

For both niraparib and olaparib, dose adjustments can be made for AEs. With olaparib, in general, the starting dose is 300 mg twice a day. The first dose reduction is to 250 mg twice a day, and the second reduction is to 200 mg twice a day. It’s a little more complicated [because] the pills come in different strengths. It’s a little easier to dose reduce with niraparib, because it comes in 100-mg capsules, and each dose reduction is a 100-mg reduction. The starting dose is either 300 mg or 200 mg, based on body weight and platelet count.
What does the American Society of Clinical Oncology (ASCO) recommend in regard to germline and somatic testing in epithelial ovarian cancer?

The ASCO guidelines have a lot of information. Basically, we know that anyone who has epithelial ovarian, fallopian tube, or primary peritoneal carcinoma should be offered germline BRCA1 and BRCA2 testing and even expanded panel testing.²⁰

For patients who don’t carry a germline pathogenic [or likely pathogenic] variant of BRCA1 or BRCA2, ASCO recommends somatic tumor testing to see whether or not those patients are candidates for maintenance with olaparib or other PARP inhibitors,²⁰,²¹ mainly because of the SOLO-1 trial.³ Anyone who is a first- or second-degree relative of a patient with ovarian cancer should be offered genetic testing.²⁰,²¹ We refer patients to our genetic counselors; I think most institutions have genetic counselors at this point.

What genetic testing guidelines does the NCCN recommend?

The NCCN’s recommendations for tumor molecular analysis include next-generation testing for BRCA1 and BRCA2 mutations and other somatic mutations; for example, the NTRK gene fusions, which are rare. They say that, in addition to BRCA1 and BRCA2 testing, other methods to evaluate homologous recombination status may be considered. The NCCN also recommends testing for mismatch repair proteins because a small set of patients with ovarian cancer will have Lynch syndrome [and testing for microsatellite instability]. Finally, according to the NCCN, additional somatic tumor testing can be done at the physician’s discretion.¹²

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Targeted Oncology™: What are the recommended approaches for relapsed/refractory DLBCL in the second-line and subsequent therapies settings?

**GOPAL:** What the NCCN [National Comprehensive Cancer Network] guidelines have for second-line therapy in nontransplant candidates is basically a dealer’s choice.¹ This patient was on R-GemOx. Polatuzumab vedotin [Polivy] with bendamustine [Treanda] and rituximab [pola-BR] is also FDA approved. Others on the list are historical lymphoma regimens, many containing platinum, and then more recently, tafasitamab [Monjuvi] plus lenalidomide [Revlimid], which is approved to treat adults who are not eligible for transplant. Other regimens used in certain circumstances include brentuximab vedotin [Adcetris], a CD30-targeted agent, and bendamustine plus rituximab, ibrutinib [Imbruvica], and lenalidomide plus rituximab. For CAR [chimeric antigen receptor] T-cell therapy, we now have 3 agents approved in the third-line space.

**CASE (continued)**

- CAR T-cell therapy was discussed as an option, but the patient declined because of the distance to nearest transplant center.
I think we all know from our practices that study data never match what we see in the clinic. My thoughts in general are that there’s more discordance between the real-world and clinical trial data because the histology in real-world data tumors is more aggressive.”

—AJAY K. GOPAL, MD

What do you think about the currently approved CAR T-cell therapies for DLBCL?
The 3 proven CAR T-cell agents for third-line therapy all have single-arm studies, but I think we all know from our practices that study data never match what we see in the clinic. My thoughts in general are that there’s more discordance between the real-world and clinical trial data because the histology in real-world data tumors is more aggressive. The studies put all these little things like you have to do X, Y, and Z, but then you’re weeding out all the patients with explosive disease and you end up getting a better-risk population, so the single-arm trials are probably not the same [as clinical practice]. For axi-cel [axicabtagene ciloleucel (Yescarta)] for example, I was part of a group that put together some real-world data, and the CR rate, which was 58% in the trial, was 42% for our study-ineligible patients.²

The median progression-free survival [PFS] was only 3 months if you were fit enough to get axi-cel, but you wouldn’t have met the eligibility criteria.² Stephen D. Smith, MD, from the Seattle Cancer Care Alliance looked at the eligibility criteria for patients who had 2 prior lines of therapy, and none of them got CAR T-cell therapy, but just meeting the eligibility to ZUMA-1 trial [NCT02348216] gave a statistically significant improved survival advantage. We never get the same results of the trial for off-trial patients, and they are probably not quite as good as what these studies tell us.

How many patients were included who had transformed follicular lymphoma (FL)?
[Sixteen patients had transformed FL]. Axicel has a label for transformed FL and liso-cel [lisoctagene maraleucel (Breyanzi)] has a label for any transformed, including DLBCL arising from indolent lymphoma. But my sense is that these patients don’t do worse. Sometimes, they’ve had more lines of therapy, which might impact their tolerability, or they’ve had many lines through their FL, then they transform and get CAR T-cell therapy. For straight-up FL, there are also published data supporting a label for 2 prior lines for axi-cel as well, but we’re not using it for many of those cases.

What are the toxicity profiles of CAR T-cell agents?
Generally, we think that axi-cel probably has a little more toxicity, both for cytokine release syndrome [CRS] and neurotoxicity.² We don’t have much real-world data for the other constructs yet, but at least the studies suggest they’re a little better tolerated for neurotoxicity and CRS.²,³,⁴

What data led to the approval of pola-BR for third-line therapy for relapsed/refractory (RR) DLBCL?
The study that got pola-BR approved [NCT02257567] was designed as a randomized phase 2 trial, so it does give you a sense of the relative benefit of adding BR, which may not have been the first thing we pull off the shelf anyway for RR DLBCL. The eligibility criteria were adults with a confirmed biopsy, at least 1 prior line of therapy, ECOG performance status of 0 to 2, and grade 1 or less peripheral neuropathy, and either transplant ineligible or failed prior autologous stem cell transplant [ASCT].⁵

[For the exclusion criteria], the patients did not have an allogeneic transplant or ASCT within 100 days, did not have transformed disease, and were transplant ineligible. The 2 arms were BR vs pola-BR with 2 patient groups with FL and DLBCL. The patients with DLBCL were given the regimen on a 21-day cycle vs a 28-day cycle for FL. The polatuzumab dose was 1.8 mg/kg intravenously.

The median for the prior lines of [therapy for both arms] was 2. Most patients had a duration of response to last prior therapy of less than 1 year or refractoriness to last prior therapy, which by definition in this trial,
was less than a PR or relapsed within 6 months. It’s not a huge surprise that this is the case with DLBCL, but the majority had refractory disease to the last therapy and minority had prior stem cell transplant.

The primary end point was objective response, and one may argue that maybe that’s not the most important end point in DLBCL, but for this trial, they showed that the pola-BR improved the overall response rate [ORR] and CR rate. The ORR was 45%. Dr Smith put together a group looking at some of the real-world data, and the ORR was pretty similar. The CR rate was lower in the real-world pola-BR data at 24% [compared with 40% in the trial].

The median PFS in the pola-BR arm from the study was 9.5 months, but the median PFS was only 2 months in the real-world data, so it’s not quite the same, but I think that’s not a surprise because of the selection criteria. I think people are probably aware of these data. So not a home run, probably, but as a stand-alone, even in the pola-BR arm, a median survival of 1 year is not fabulous.

I think this is what happens in aggressive malignancies when you don’t have study selection criteria, so what I take away from these studies is that I can’t always apply it to my patients. There is probably more benefit for pola-BR than BR, but you probably aren’t going to get on the pola-BR curve unless you have a fit patient who might have met the eligibility criteria.

The main point for adverse events [AEs] is that there was more discontinuation on the pola-BR arm of about one-third. The main AE monitored was peripheral neuropathy.

What data led to the approval of tafasitamab plus lenalidomide?

Tafasitamab is an Fc-enhanced anti-CD19 monoclonal antibody [mAb] and is probably more similar to the way obinutuzumab [Gazyva] is optimized, so more of the Fc receptor and less of the complement fixation. We don’t exactly know how lenalidomide works, but there’s some hypothesized mechanisms. The single-arm L-MIND study [NCT02399085] led to the approval of tafasitamab plus lenalidomide.

I would just be cautious about any single-arm studies, particularly in aggressive malignancies like DLBCL in terms of the real-world results, which we have not seen yet. The study was for patients with 1 to 3 prior regimens who were transplant ineligible. Those who were primary refractory were excluded, so they took out the highest of the high-risk group. I’m not being particularly critical of any agent or trial, but there is a theme of certain high-risk subsets getting excluded, but these are the ones who are the most in need.

Tafasitamab, for those who have given it, has an induction dosing at day 1, 8, 15, and 22 for the first 3 cycles, then every other week for cycle 4 through 12. It’s 25 mg per day for lenalidomide from day 1 through 21. In my experience, lenalidomide gets tougher as patients get older, and I also think it’s tougher in patients with lymphoma for some reason, than in patients with myeloma. I don’t have any myeloma cases, but it just seems that way to me. The tafasitamab continues after 12 cycles indefinitely, but the lenalidomide stops. The primary end point was ORR.

Reading the fine print of all these trials, they don’t always tell you the whole story of the patient population and who was not included. The median prior lines of therapy for the L-MIND trial were 2, so like the pola-BR trial from that perspective. A minority of patients had had a prior stem cell transplant, again like the pola-BR trial. A lower number compared with the pola-BR trial were refractory to their last prior therapy by 6 months, but it is not appropriate to compare across studies.

The CR rate was 40%, PR was 17.5%, and the median duration of response [was 43.9 months], though I’m itching to see real-world data to see if the patients were chosen in a way to get a long duration of response. I’m always skeptical of study data, my own data included.

The median PFS was about 1 year in this population, and interestingly, the overall survival [OS] was eye popping at 33.5 months. Again, taking care of a lot of patients with DLBCL, I just wonder who those patients were and if they are the ones we see in our clinic with explosive refractory disease. These are the data, but I think we need to see more real-world information.

What study data led to the approval of loncastuximab tesirine?

Loncastuximab tesirine [Zynlonta] is another antibody-drug conjugate. It has a different PBD [pyrrolobenzodiazepine] payload and AE profile. Polatuzumab and brentuximab have the MMAE [monomethyl auristatin E] vedotin for example, and the same general principle [applies to loncastuximab] that binds to CD19 and is internalized and causes PBD to be released, which causes DNA cross-links and eventual cell death.

The LOTUS-2 trial [NCT03589469] was, again, a single-arm trial that led to the approval of loncastuximab. I read the protocol before as published. So there were some little exclusions in there; for example, you couldn’t have any mass that was 10 cm or larger, so that’s a big lymphoma mass, but it still took out some patients. There were the usual things of getting 10 unstained slides and for patients that have rapidly progressive disease in whom you can’t get another biopsy, those could not go on the study. All the studies do this, so I’m just saying, it’s not real-world scenarios where you must treat people quickly.
Every 3 weeks, the patients got a dose of 150 μg/kg for the first 2 cycles, then after 2 cycles, the dose is dropped to 75 μg/kg, and they get it for up to a year. They found that by dropping this dose after the first 2 cycles, you get less AEs.11

I will give credit that this was a bit of a larger study, so 145 patients, and there were some who had double, triple, and transformed disease. They might have been a more indolent because it’s hard to get on a trial with a relapsed double-hit lymphoma that’s exploding. They had 3 prior regimens, so more lines of therapy than the other studies.

How did patients do on the LOTUS-2 trial? The ORR came quickly and was at 48%; half of those were PRs and half were CRs. There was a little less follow-up on this study, but the CRs, not surprisingly, were maintained. The median number of cycles to response was relatively short, at 4.5 cycles. We always have to be cautious in interpreting subgroup analyses because these studies are not powered to show differences in these subgroups. It is not clear that any one particular group did worse, but perhaps refractory disease, not surprisingly, did worse than relapsed disease.

The most recent reported median duration of response was 13.4 months, and for those with CR it was not reached; whether this is drug related or tumor related is hard to know. A longer follow-up had similar data for the median PFS, [which was 4.9 months (95% CI, 2.9-8.3)] and median OS [was 9.9 months (95% CI, 6.7-11.5)]. For subsequent therapy, I think we don’t know the answers. My 84-year-old patient got CAR T-cell therapy after tafasitamab plus lenalidomide, and was not a transplant candidate, had basically stable disease that lasted for a few months. Then he went on a clinical trial with a bispecific antibody, which gave him stable disease, and then I referred him to get CAR T-cell therapy. He got biopsy, he still had CD19, so he got a CAR T-cell agent and got about 9 months of remission out of that.

Unfortunately, he relapsed, got re-biopsied, still had CD19, and now I’m treating him with loncastuximab. I’ve reimaged him and he has about a 40% reduction in his adenopathy, but he’s not at PR yet. A patient can get 3 lines of anti-CD19 therapy and I guess none of them completely did the trick so far, but I’m hoping we’re going to have more data in the future on this.

For loncastuximab, the protein dose is small and it’s probably related to the potency or toxicity of the payload, so you’re not getting a lot of antibody dose there, for what it’s worth. Peripheral edema is the main thing to watch for, and it tends to kick in later, after about cycle 3. I’ve talked to folks from the company to try to find what’s the mechanism. I don’t think anybody completely understands it. It’s related to the payload, presumably, but patients get peripheral edema, and pre-treatment with steroids seems to help some.10 My patient is not having any issues with edema, but he’s getting a little bit of borderline neutropenia and the absolute neutrophil count is around 1100.

If you use this drug, it’s important to be aware of the peripheral edema and the dexamethasone premedication for a few days prior, but that’s sometimes tougher than the chemotherapy, especially in older patients.

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TUMOR LYSIS SYNDROME

Roundtable Discussion: Risk-Based Prevention of Tumor Lysis Syndrome in Hematologic Malignancies

DISCUSSION QUESTION

In general, what tumor lysis syndrome (TLS) risk factors are most significant to you?

ALEGRIA: I am in Jacksonville and predominantly the population of [patients] I deal with have CLL [chronic lymphocytic leukemia] and multiple myeloma. When I’m assessing patients with CLL, I’m looking at their white blood cell count and tumor burden overall. What general history do they have? Where is the LDH [lactate dehydrogenase] already at? What are we looking at? What drugs are we going to put them on? Am I going to prophylactically start allopurinol? Do they need to be hospitalized? Are we going to do something prior to starting venetoclax [Venclexta] and reduce some of that tumor burden, and then not hospitalize after the BCL2 inhibitor? So, I just look at the overall patient and their disease burden.

PINILLA-IBARZ: I agree, sometimes it depends on the population you’re dealing with.

HUSSEIN: I definitely consider the type of disease and treatment. I usually check comprehensive metabolic panel and uric acid to have an idea about the baseline and assess how aggressive we need to be with treatment. I check the kidney function too.

WANG: Yes, same [here]. I’m less concerned with BTK [Bruton tyrosine kinase] inhibitors even though it can happen, but with venetoclax/obinutuzumab [Gazyva], particularly, that’s what I’m most concerned about. How much the disease burden is, what drugs we use, and whether they have any preexisting kidney dysfunctions are all factors I consider in CLL or SLL [small lymphocytic lymphoma] for TLS treatment or prophylaxis.

KHARFAN DABAJA: I think a group of patients, for instance those with CLL, have this transformation where they have this rapid proliferating tumors with masses of more than 5 cm or maybe 10 cm. They are at high risk for TLS. I think both the proliferative index and baseline serum creatinine are also important.

HURTADO: Yes, I think it depends on what kind of pathology we see and the use of the new medications, [such as] venetoclax and BTK inhibitors. Usually, I pay close attention to white blood cell count because a lot of patients get into complications because of that. Also, for the tumor burden, if I have large nodal disease that is going to be debulked rather quickly with whatever regimen I’m using, I pay close attention.

PINILLA-IBARZ: I think sometimes we believe that the [clinical manifestations] are going to happen right away, but we may forget or not realize that they may come 12 to 72 hours after initiation of these types of therapies. It depends on the dynamic of the treatment that we are establishing. Some of the consequences of these metabolic [disorders] could be
nausea, vomiting, diarrhea, anorexia, weakness, lethargy, cardiac dysrhythmias, hematuria, seizures, muscle cramps, and syncope. Keep in mind [that older patients] may experience this after the first 24 hours.

DISCUSSION QUESTIONS

• In your experience, what clinical manifestations of TLS have been most problematic or challenging in the short term? What about in the long term?
• When you hear the term TLS prophylaxis, what comes to mind?

THOMASSEN: I’ve seen some patients with increased creatinine. It was problematic in the short term for 1 patient I can think of who ended up needing dialysis because we weren’t able to correct it prior. But once he got dialysis, he was OK. That was challenging and problematic in both the short and long term.

PINILLA-IBARZ: I think you give a [good] example. Acute renal failure and the consequence of that could be an important one.

AMIN: Short term is mainly acute renal failure and hypercalcemia, and then risk of cardiac arrhythmia from that. Long term is mainly chronic renal failure or at least chronic kidney disease. Sometimes even with 1 treatment the patient ends up in rehabilitation.

I had a patient who had diffuse large B-cell lymphoma [DLBCL] with a borderline age. After the first treatment, she ended up in a hospital and had a prolonged recovery. By the time she recovered, her lymphoma was so bad that she... died because the disease was too advanced. That’s the problem with a long-term issue, if [a patient] has borderline heart function, kidney function, and is in their 80s. This is what we see in Florida, mainly.

PINILLA-IBARZ: You bring up a good point. It depends on the biology of the disease and how soon you need to retreat those patients. I have experience with some patients with CLL who you treat and they get TLS, but it takes a long time until they require therapy. But patients with lymphoma are going to come back to you soon.

PARAS: I see] the same as what my other colleagues have said, though mainly we deal with the older population with a lot of comorbidities. The main issue is that whenever they go into renal failure from TLS, you would like to hydrate them, but then there’s a challenge that you might push them to congestive heart failure. A lot of times the renal failure reverses, but it takes longer, especially if they’re older [patients]. Sometimes if they go to congestive heart failure or renal failure, they get chronic renal failure or have a heart attack. Sometimes they don’t fully recover from the initial injury that was brought about by the chemotherapy. I’ve seen it a lot of times where they develop complications from chemotherapy and one of them is TLS.

MURTHY: When I think prophylaxis, we all think allopurinol. But something else we really think about is not necessarily prophylaxis but more like hypervigilance in terms of monitoring the patients. Essentially, it is the prophylactic measures that we take: close monitoring, hydration, monitoring the laboratory results very frequently and determining whether in-patient hospitalization is the safest thing. So I think of all those things when I hear TLS prophylaxis.

PINILLA-IBARZ: I think it’s a good point. It’s everything that comes together.

GLIGICH: I agree. Starting allopurinol early is very important. A large portion of what we tend to forget is the amount of IV [intravenous] hydration that these patients need. Usually, if they are high risk, I tend to start them anywhere from 300 mL to 500 mL an hour, because if you look at the data that’s what prevents renal disease.

One of the things that we didn’t mention or didn’t home in on in the past is about what the risk factors for TLS are. I treat a lot of DLBCL and high-risk lymphomas, and the Ki-67 score is huge for me, but you can’t focus on 1 particular point [such as] the white blood cell count, the kidney dysfunction, or the Ki-67 score. You need to take a look at the clinical picture all together, and if you’re missing 1 of these factors, you can’t put the pieces together. So I think everything is extremely crucial here.

PINILLA-IBARZ: I completely agree, and I was touching upon the fact that every patient is different. As you mentioned, you must get this global approach about these specific things. For Ki-67, we have 80% to 90% in this setting; most of the time you’re going to see a high LDH, but not always. This disease is growing fast, and as soon as you touch it, they are going to be [in a tough situation], because it depends on what you do. But I think it’s a great point.

CARTWRIGHT: I agree, too. It’s more of using judgment and weighing multiple factors [such as] the underlying comorbidities and patient’s age. Hydration and allopurinol are the first things that come to mind.

PINILLA-IBARZ: Something that always provoked me is the fact that even if we do everything sometimes we still have problems.
NAKKA: We have the tumor factors, patient factors, and treatment-related issues that could determine if a patient is high risk or low risk. But I’m thinking that one of the unmet needs is a marker that tells us if the marker is high, we give prophylaxis, let’s say IV fluids or allopurinol. Or if the marker is higher, then you give IV fluids and rasburicase [Elitek] with the first treatment. We have multiple things to put together, but it’s still hit or miss.

PINILLA-IBARZ: We can do our best. I think we may be familiar with the classification of TLS in the venetoclax [treatment guide, based on absolute lymphocyte count of] less than 25, more than 25, and so on.² I think it’s, as you all mentioned, a conglomerate of issues that must be taken on a patient-by-patient basis. Otherwise, it’s tricky.

ALEGRIA: One area that I’m still a little unsure on—and it’s an area that we’re delving into a little bit more with BCL2 inhibitors regarding multiple myeloma—what makes them potentially higher risk for TLS? Is it just the bone marrow involvement? Is it extramedullary disease? What defines them as being a higher risk when we’re using that kind of drug? I think that’s an area that isn’t too well known.

PINILLA-IBARZ: We don’t have specific markers that will tell you what the higher risk is. That’s the reason we try to use prophylaxis.

THOMASSEN: About being hypervigilant, I think sometimes in these cases maybe we think, “Oh, it’s not going to happen,” and we put it out of our mind. Then you’re caught off-guard a little bit. So maybe taking the extra time to be super thorough in the assessment of the patient, not taking anything for granted, and making sure that the whole team is involved can prevent it.

PINILLA-IBARZ: I think it’s a good point. Once again, I think sometimes we get caught off-guard because we may not have enough monitoring capacity.

DISCUSSION QUESTION

Have you used rasburicase? If so, what was your experience with it?

AMIN: I have used it in a patient with CLL who was getting venetoclax and had a very high tumor burden, a patient with AML [acute myeloid leukemia], and a patient with Burkitt lymphoma. I have used it both in the outpatient and inpatient setting. Usually, the dose requirement in a trial is high, maybe 2 doses or more to bring down the uric acid to the below normal level, most of the time. You’ll catch it with hydration, and allopurinol on top of that….I have never seen the drug not work, and it always has very good efficacy.

For outpatient [cases], I have no problem because I always get authorization from insurance and give it. But, inpatient, they don’t have it in the formulary, so I beg the pharmacy to do it, and it sometimes takes a few hours or a day to get it. That’s always a problem.

PARAS: I mainly treat solid tumors, but I have a few experiences. One is a patient with bulky DLBCL. Then, another had AML and I treated them with venetoclax, but the uric acid went up at treatment, though his numbers were not elevated to begin with, and he went to renal failure, so I decided to put him on rasburicase. Both did well, but I usually have intermediate or low-grade, low-risk cases.

PINILLA-IBARZ: What kind of dosing do you use? Is it the 0.2 mg/kg or the flat dose?

MURTHY: We use the flat dose, and I’ve had no issues. Frankly, the only issue that I had was getting a little pushback from pharmacy about giving it. But other than that, it is very tolerable and works fast. I’ve used it in Burkitt, AML, and ALL. I’m a believer.

PINILLA-IBARZ: Do you use 3 mg or 6 mg?

MURTHY: [I use] 6 mg.

GLIGICH: I haven’t done 3 mg because I always have problems with pharmacy. They only give me the limited dose, 1.5 mg. The patients always respond very well, and I want to call back pharmacy the following day and ask them to give me more. The uric acid levels plummet, and they do well.

HURTADO: I have used it. I never had any adverse event from it. I have used it in AML, CLL, and lymphomas as well. I think the biggest issue is I practice in a community-based public-funded institution. I think they go a lot by the guidelines. If you try to use more clinical judgment, they might [push back] if the patient is not particularly high risk. Let’s say you think that the patient already had preexisting renal disease and they might benefit from prophylaxis—they might give you some pushback. Generally, if the patient is
high risk, or has AML, or something [such as] that, the pharmacy will dispense it to you.

**KUNTA:** I don’t have issues with the pharmacy because we have our own dispensing pharmacy. For the most part, I have had excellent results. I [use it for] DLBCL or CLL with a high white cell count, or sometimes very bulky follicular lymphoma. I use the flat dose of 3 mg. After the first cycle, I haven’t had to use it because uric acid plummets.

**NAKKA:** I use it both in the inpatient and outpatient settings. For AML and CLL, I first treated them inpatient with venetoclax. But [recently] I’ve been treating them outpatient, and I give the obinutuzumab before and then start venetoclax and go up on the ramp dosage. I get the authorization for rasburicase before.

**PINILLA-IBARZ:** So you use [rasburicase] before obinutuzumab. Before the debulking is when you really have the high tumor burden. I agree with you. [For obinutuzumab,] it’s even worse than what we have with venetoclax, so we should be more aware of the possibility of this trouble.

**DISCUSSION QUESTION**

Does your institution have a standard order set/protocol for TLS? What does it look like?

**PINILLA-IBARZ:** I have this discussion in my own center. We get together with pharmacy to reestablish a protocol of where, when, and how we can use the drug without having to fight, “Oh, I want to have this,” “No, it’s not indicated.”

**CARTWRIGHT:** There’s no standard order set that I’m aware of. I don’t even think in the United States oncology [guidelines]. There may be, but I haven’t used it. The uric acid is sometimes hard to get done stat. The G6PD [glucose-6-phosphate dehydrogenase] too, you can’t order it stat.

**PINILLA-IBARZ:** Absolutely. We fight sometimes with the pharmacies with that because if you have...an emergency, there is no time.

**CARTWRIGHT:** Mainly for [a Black] patient or somebody who you would be hesitant. But I don’t think we have time to check for G6PD.

**HUSSEIN:** We don’t have a protocol per se; we do have a rasburicase order set; it’s up to the physician, and we check G6PD. You must make a judgment call because if you need to get that you have to order it right away.

**ALEGRIA:** I am clinic based, so there is no order set for me for TLS within the clinic itself....For outpatient clinic, there is none.

**MURTHY:** We don’t really have a set order set; they are standard. We try to check G6PD, but obviously the timing is really the biggest issue. How are you going to get it back in time to make a meaningful intervention? I think when we decide to give rasburicase we’re usually discussing with pharmacy in real time rather than having a set protocol in place.

**PINILLA-IBARZ:** Right. So they don’t ask you specifically to have a series of criteria?

**MURTHY:** No, it’s mostly case by case because these are oncologic emergencies, so there are always different factors rather than [doing] things per protocol.

**KHFARAN DABAJA:** With rasburicase specifically, it is mostly reactive rather than proactive, as Dr Murthy mentioned. The basic orders are mostly for prophylaxis with allopurinol, but we don’t have rasburicase as a prophylaxis order set.

**THOMASSEN:** We have an order set where I work at the University of Miami, specifically for inpatients. We often use rasburicase, especially if the patient is at high risk. We use the standard dose of 3 mg and it’s been effective from what we’ve seen. Typically, though, if they’re releasing the order set it’s because the patient is already experiencing TLS. We have the prophylactic set, and then if they’re experiencing [TLS, the questions are] what to do from there and how frequently to draw the laboratory results, and are any additional orders needed?

**CARTWRIGHT:** Do you have order sets at Moffitt Cancer Center?

**PINILLA-IBARZ:** Yes, we do. It is very similar to the University of Miami one. We have a standard procedure where they ask you a series of questions like those for G6PD, and you have to accomplish the high-risk criteria, one of which is CLL because almost in all cases these patients have hyperleukocytosis, and it is the reason we can easily use it.

I was involved in those guidelines and we studied a 3-mg vs a 6-mg dose because it’s something that has been debated. We decided to go with the 3 mg for prophylaxis, and for TLS we go with 6 mg.

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**FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM**
Targeted Oncology™: What is the evidence for adding abemaciclib (Verzenio) to endocrine therapy for high-risk early-stage breast cancer?

DIETRICH: The [evidence for this comes from the] monarchE study [NCT03155997], which was a very large clinical trial with almost 6000 patients enrolled. The study had 2 cohorts for hormone receptor–positive, HER2-negative, high-risk, early-stage breast cancer. Cohort 1 was determined to be high-risk based on clinical and pathological features, such as more than 4 positive lymph nodes, or 1 to 3 positive axillary lymph nodes, and either grade 3 disease or a large primary tumor.

Patients in cohort 2 were determined as high-risk based on Ki-67 as a marker of proliferation, with 1 to 3 positive lymph nodes, Ki-67 [greater than or equal to] 20%, and no grade 3 disease or tumors [greater than or equal to] 5 cm. So this patient would fall into cohort 2, which is FDA approved. Patients in the study were randomized 1:1 to endocrine therapy with or without abemaciclib for 2 years, with a clinical follow-up period of 3 to 8 years [5-10 years in total].

My definition of a high-risk patient is combined with [whether there is a need for] chemotherapy. That is, I consider every patient I give chemotherapy to be clinically high risk.
with 1 to 3 positive lymph nodes and 60% with more than 4. The groups were also balanced with respect to premenopausal and postmenopausal status. Most patients had a primary tumor of intermediate size [2-5 cm], [Approximately] one-third of the patients had low Ki-67, 50% had Ki-67 [greater than or equal to] 50%, and an insignificant number had unavailable Ki-67 levels.1,2

The [invasive disease-free survival data were] interesting. At 24 months, it was [approximately] 2.7%. At 3 years, there was a 5.4% difference between the 2 groups.1 So the difference between the 2 groups is increasing after treatment completion, with sort of a memory effect. This–5.4%–is about the benefit we would expect from an adjuvant aromatase inhibitor [AI] in this setting. The risk reduction for an invasive disease-free survival event was [approximately] 30% with the addition of abemaciclib, and this was highly statistically significant [HR, 0.696; 95% CI, 0.588-0.823; nominal P < .0001].1

What were the results of the subgroup analysis in this study?

Not surprisingly, [the subgroup analysis showed] that when looking at tumor growth and metastatic potential, abemaciclib confers a clear benefit, independent of lymph node status. Most patients with higher-grade tumors—grade 2 and 3—benefited from the addition of abemaciclib, [whereas] the events for patients with grade 1 tumors were relatively balanced between the 2 groups.

There was a benefit to adding abemaciclib for smaller tumors [<2 cm] [and] larger tumors [≥5 cm]. Neoadjuvant and adjuvant therapy had overlapping confidence intervals, and combination treatment was favored for premenopausal patients. Typically, we like to get these patients to be postmenopausal with treatment, independent of region, and younger patients tended to have improved outcomes. Progesterone receptor [PR] discordance did not play a big role, and we’ve seen this in the metastatic setting. PR discordance is not necessarily an obstacle for CDK4/6 sensitivity. Finally, the performance status and stage also favored the addition of abemaciclib.1

More importantly: Is invasive disease-free survival a good surrogate marker? [In terms of thinking about OS], the marker that makes me more excited is the distant relapse-free survival. Is it inside the chest wall [or] anywhere it can be approached curatively again?

How was disease relapse impacted by this treatment?

It’s very clear many relapses in this study were with distant metastases, with a 4.2% delta favoring abemaciclib for distant relapse-free survival at 3 years, and those are not salvageable for curative intent treatment. The relative risk reduction was almost 1:1 between invasive disease-free survival and distant relapse-free survival,1,3 so most of these events happen outside the chest wall. This is owed to a good extent to radiation therapy, but it clearly gives the study more credibility for usefulness in the early-line setting.

Looking at both markers, this is a benefit that not only maintains past the treatment period but is actually extending.4 So there is a degree of tumor suppression that leads to a crippling impact on the ability for tumor formation, or at least a delaying impact, here for a cancer-free survival in the long run. So we’ll want to see longer-term data for this study. The concordance between invasive disease-free and distant relapse-free survival gives you an outlook toward the survival impact the study may have.

How does the Ki-67 biomarker impact patient outcomes?

There is an interesting aspect when we think about the current FDA label. Cohort 2 is currently approved for elevated Ki-67, and there is a benefit of [approximately] 6% with abemaciclib at 3 years. There is also an almost identical benefit for invasive [disease-free] and distant-free survival, with a 37% risk reduction for the Ki-67–high group, not surprisingly. The survival curves seem to be running out in parallel in later time points, but this is not yet ready for analysis. So roughly the same amount of relative risk reduction—1:3.1,3

One of the central features of the Ki-67 oncotype is an mRNA-based evaluation of its levels, so it’s not surprising that the prognostic impact of genomic testing and Ki-67 correlate. Prognostically, patients with low Ki-67 levels fare better than patients with high Ki-67 levels. But interestingly, [although] this is a prognostic marker, the abemaciclib benefit was identical between the 2 cohorts, with hazard ratios of 0.62 for the high risk and 0.70 for the low risk. This is especially notable considering this is a large patient trial, with almost 2000 patients in each cohort,1,3 so I was surprised when the FDA did not consider Ki-67–low patients in the clinical high-risk setting for potential approval.

What other data should clinicians know about?

The OS data are very immature. There seems to be a slight trend favoring abemaciclib, but it is not ready for interpretation. I think this is the rationale for distant disease-free survival being the decision-making driver. There were several other features analyzed, as well. The efficacy data also favored the addition of abemaciclib across the different subgroups. The question is: What about the impact on tolerability?

There’s the clearly established safety profile of abemaciclib, with [gastrointestinal] adverse events [AEs] of diarrhea being at the forefront, which levels out after

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the first couple of cycles and can be managed proactively with the addition of antimotility agents. The number of grade 3/4 toxicities were substantially lower than in earlier trials. The management has gotten a lot better. These toxicities were higher than on endocrine therapy alone, but this is one of those AEs that can be managed. Another important toxicity was cytopenia.

One of the factors that was the most interesting—and is one of the most frequent clinical challenges I face in practice—were the aromatase inhibitor (AI)–related AEs [hot flashes, arthralgias, and mood swings]. These were significantly improved by the addition of abemaciclib. For example, 20% of any-grade arthralgias compared with 31% for endocrine therapy alone. I have to say, in my clinic, those numbers are probably higher.

There’s clearly a trend, and the idea is that abemaciclib has an anti-inflammatory component to it that may be mitigating some of these AEs. This wasn’t seen as much in the metastatic setting, but it’s certainly of interest in terms of tolerance. I just had a patient that came off a clinical study that had evaluated CDK4/6 inhibitors in the adjuvant setting. The patient went back on because [she was unable to tolerate the AIs] without the CDK4/6 inhibitors. So we’re working on this for an intermediate strategy in the interim.

The discontinuation rates were 16% for abemaciclib, 6.2% for the abemaciclib and endocrine therapy combination, and only 0.8% for endocrine therapy alone. That’s not representative of what we see in my clinic, and I’m not sure you’re able to get 99.2% of your patients through endocrine therapy. Those are very motivated trial participants here.

How did the FDA approval of abemaciclib impact the use of that drug?
The FDA approved abemaciclib with endocrine therapy on October 12, [2021]. Interestingly, the approval was either with tamoxifen or an [AI]. If you remember, ribociclib [ Kisqali ] was previously tested with tamoxifen, and there was a substantial increase in QTc prolongation, so it was not approved as a combination therapy.

However, with abemaciclib, it’s moved into a tolerance spectrum—probably related to the QTc prolonging impact being mediated by CDK6—where abemaciclib is not as impactful as on CDK4. The broader FDA definition is for hormone receptor–positive, HER2-negative, node-positive breast cancer, with a Ki-67 of greater than 20%, as determined by an FDA-approved test. The Ki-67 IHC MIB-1 pharmDX Dako assay is the approved companion diagnostic, but this can be done on several platforms. This marker should be tested for every patient with breast cancer.

As a result of the FDA approval, the American Society of Clinical Oncology [ASCO] guidelines had a rapid recommendation update, where 2 years of abemaciclib at the standard dose of 150 mg twice daily plus endocrine therapy may be offered to patients with hormone receptor–positive, HER2-negative, node-positive breast cancer, with a high risk and a Ki-67 score greater than 20%. That is, the guideline echoes the FDA label.

However, the ASCO panel is also including abemaciclib plus endocrine therapy for 4 years for patients who were in the rest of the intent-to-treat population, with hormone receptor–positive, node-positive, early breast cancer at high risk of recurrence, with 4 positive lymph nodes, or 1 to 3 positive lymph nodes, with additional high-risk features of histologic grade 3 disease, tumor size greater than 5 cm, and a Ki-67 of 20%. This basically says abemaciclib is recommended for all clinically high-risk lymph node–positive disease. However, [because] the absolute benefit for these patients were not as substantial and the number of patients was smaller, patient preferences should be taken into consideration.
MULTIPLE MYELOMA

Roundtable Discussion: Madan and Participants Debate Treatment Options for a Patient With Multiple Myeloma

CASE SUMMARY

In 2017, a 55-year-old Black man 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], and dexamethasone) for 4 cycles, followed by autologous stem cell transplant. The patient achieved a very good partial response and received lenalidomide maintenance, planned until progression.

DISCUSSION QUESTIONS

• What possible treatments are available for this patient with multiple myeloma?
• Which 3- and 4-drug regimens do you prefer?

AMBICA: I don’t understand the rationale for going with carfilzomib [Kyprolis] in this setting. Which data are you going with in standard risk?

MADAN: The data essentially come from the FORTE trial [NCT02203643]. The FORTE trial was 3 arms. One of the arms received KRd [carfilzomib, lenalidomide, and dexamethasone] with transplant followed by consolidation.

The second arm received only KRd for 12 cycles. The third arm received only KCd [carfilzomib, cyclophosphamide, and dexamethasone]. KCd was inferior, so we can leave that out. Within those 2 arms, KRd with transplant followed by KRd, had deep remission and deep response rates. That’s one.

We don’t have a trial comparing KRd vs VRd in patients undergoing stem cell transplant. But if you look, we have a trial showing [a] doubling of progression-free survival [PFS] advantage when Kd [carfilzomib and dexamethasone] was compared with Vd [bortezomib and dexamethasone] head-to-head in the relapsed/refractory myeloma setting. The PFS with Kd was 18.7 months vs 9.4 months [with Vd]. Again, this is the relapse setting. It’s just based on my experience and looking at all the data I can get.

AMBICA: For the quadruplet regimen right now, it’s in the high-risk subgroup, at least in the National Comprehensive Cancer Network [NCCN] guidelines, so we can appeal it. Otherwise, it’s hard to get insurance authorization for standard-risk patients right now.

MADAN: What is also very important is—it doesn’t happen too often, but every now and then—despite everything you do, one of your patients is going to have very bad neuropathy from the bortezomib. Recently, I had

continued on page 89
For adults with intermediate- or high-risk myelofibrosis (MF)

WHAT YOU DO TODAY CAN IMPACT THEIR TOMORROW

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

Important Safety Information

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to seek early treatment.
- Avoid concomitant use with fluconazole doses greater than 200 mg. Dose reductions may be required.
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections.
- The most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and fatigue.
- In an open-label study of patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi, the percentage of patients who achieved a ≥35% reduction in spleen volume at ≥12 weeks was 31% for patients receiving Jakafi and 0% for patients receiving placebo.
- In COMFORT-I, the primary endpoint was ≥35% reduction in spleen volume at 24 weeks. The percentage of patients who achieved this endpoint was 20.5% for patients receiving Jakafi at 0.25 mg, 39.1% for patients receiving Jakafi at 0.50 mg, and 0.7% for patients receiving placebo. This difference was statistically significant (p < 0.0001).

References:
**Important Safety Information**

Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis.

- **Indications and Usage**
  - Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are modified.
  - Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
  - Serious bacterial, mycobacterial, fungal and viral infections have occurred.
  - Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor alanine aminotransferase and aspartate aminotransferase have been increased in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated.
  - Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and cutaneous T-cell lymphoma have occurred among patients with chronic myeloid leukemia in chronic phase (CML-CP) or in patients with myelofibrosis (MF). Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose.
  - Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess serum cholesterol, triglycerides, and low-density lipoprotein cholesterol before initiating Jakafi and periodically during treatment.
  - Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment. If PML is suspected, stop Jakafi and evaluate for PML using a sensitive diagnostic test. If PML is confirmed, patients should discontinue Jakafi.
  - Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors.
  - In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥20%) were diarrhea, pyrexia, and nasal congestion. The most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and viral infections.
  - Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.
  - Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose.

**COMFORT-I Primary Endpoint**

42% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24 vs 0.7% of patients receiving placebo (P < 0.0001)²

**COMFORT-I Secondary Endpoint**

46% of patients receiving Jakafi achieved a ≥50% improvement in Total Symptom Score (TSS) at week 24 vs 5% of patients receiving placebo (P < 0.0001)²

**COMFORT-I 5-year analysis: Jakafi and placebo**

- At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo.
- Overall survival was a prespecified secondary endpoint in COMFORT-I.
- Jakafi 5-year overall survival probability was 51%.

**Intervene with Jakafi at diagnosis in appropriate patients with MF**

STARTWITHJAKAFI.COM

**References:**


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**Intervene with Jakafi at diagnosis in appropriate patients with MF**

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**References:**


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Herpes Zoster

Jakafi for signs and symptoms of active tuberculosis and Tuberculosis prophylactic antibiotics according to clinical guidelines.

BRIEF SUMMARY:

Prescribing Information

cause thrombocytopenia, anemia and neutropenia.

Chronic Graft-Versus-Host Disease Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older. Chronic Graft-Versus-Host Disease Jakafi is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Adverse Reactions (6.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2.7) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2) in Full Prescribing Information]. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

Tuberculosis

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

Progressive Multifocal Leuкоencephalopathy

Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. Hepatitis B Hepatitis B viral load (HBeAg-negative) is increased with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, D/C, or multi-organ failure. If any of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. Do not begin or interrupt therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [see Dosage and Administration (2.7) in Full Prescribing Information], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. Non-Melanoma Skin Cancer (NMSC) Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. Lipid Elevations Treatment with Jakafi has been associated with alterations in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides [see Adverse Reactions (6.1) in Full Prescribing Information]. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 6-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

Major Adverse Cardiovascular Events (MACE) Jakafi has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks to the individual prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps they should take. Thrombosis Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. Secondary Malignancies Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2]. Thrombocytopenia and anemia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled double-blinded studies [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse Reactions in the Double-blind, Placebo-controlled Study During Randomized Treatment

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (247)</th>
<th>Placebo (185)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>All (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>All (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Bruisingb</td>
<td>23 &lt; 0</td>
<td>15 0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 &lt; 1</td>
<td>7 0</td>
</tr>
<tr>
<td>Headache</td>
<td>15 &lt; 1</td>
<td>5 0</td>
</tr>
<tr>
<td>New Infections</td>
<td>9 &lt; 0 &lt; 1</td>
<td>5 0</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7 &lt; 1 &lt; 1</td>
<td>1 0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 &lt; 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2 &lt; 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
* includes cytopenia, ecchymosis, hematoma, infection site hematoma, perianal hematoma, vesiculopustule site hematoma, increased tendency to bruise, petechial, purpuric
* includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labirithitis
* includes urinary tract infection, cystitis, ureospinus, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
* includes weight increased, abnormal weight gain
* includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Reactions: Anemia

In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in the Jakafi group compared to 7.4 units in the placebo group for patients treated with Jakafi. Thrombocytopenia In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose interruption. The median time to recovery of platelet counts above 50 × 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation
of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving placebo. Studies of patients with a platelet count of 100 × 109/L to 200 × 109/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 × 109/L (17% versus 7%). Neutropenia in the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=60)</th>
<th>Placebo (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3/4 (%)</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline

Additional Data from the Placebo-Controlled Study
- 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with Grade 1 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Polycythemia Vera In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see Clinical Studies (14.2) in Full Prescribing Information]. The most frequent nonhematologic adverse reaction occurring up to Week 32 was grade 1 mucositis (27% in patients treated with Jakafi and 21% in patients receiving placebo).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=71)</th>
<th>Best Available Therapy (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Spasms</td>
<td>12 ≤ 1%</td>
<td>5 ≥ 1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 ≤ 1%</td>
<td>3 ≥ 1%</td>
</tr>
</tbody>
</table>

*Presented laboratory abnormalities are listed in Table 6 below

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 ≤ 1%</td>
<td>58 ≥ 1%</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 ≤ 1%</td>
<td>23 ≥ 1%</td>
<td></td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline

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

Clinical relevant laboratory abnormalities are shown in Table 4.

Table 5: Acute Graft-Versus-Host Disease: Nonhematologic Adverse Reactions Occurring in ≥ 5% of Patients in the Open-Label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=151)</th>
<th>Best Available Therapy (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td></td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 ≤ 1%</td>
<td>13 ≥ 1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 ≤ 1%</td>
<td>13 ≥ 1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 ≤ 1%</td>
<td>12 ≥ 1%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15 ≤ 1%</td>
<td>13 ≥ 1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 ≤ 1%</td>
<td>13 ≥ 1%</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>15 ≤ 1%</td>
<td>13 ≥ 1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 ≤ 1%</td>
<td>13 ≥ 1%</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>6 ≤ 1%</td>
<td>0 ≥ 1%</td>
</tr>
</tbody>
</table>

*Presented laboratory abnormalities are listed in Table 6 below

Table 6: Acute Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 ≤ 1%</td>
<td>58 ≥ 1%</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 ≤ 1%</td>
<td>23 ≥ 1%</td>
<td></td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline

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

Table 7: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>32 ≤ 13%</td>
<td>27 ≥ 13%</td>
<td>23 ≥ 13%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 ≤ 20%</td>
<td>56 ≥ 20%</td>
<td>54 ≥ 20%</td>
</tr>
</tbody>
</table>

*Presented laboratory abnormalities are listed in Table 7 below

Table 8: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>71 ≤ 3%</td>
<td>74 ≥ 3%</td>
<td>76 ≥ 3%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>59 ≤ 3%</td>
<td>61 ≥ 3%</td>
<td>63 ≥ 3%</td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline

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

Clinical relevant laboratory abnormalities are shown in Table 8.

Table 9: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>71 ≤ 3%</td>
<td>74 ≥ 3%</td>
<td>76 ≥ 3%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>59 ≤ 3%</td>
<td>61 ≥ 3%</td>
<td>63 ≥ 3%</td>
</tr>
</tbody>
</table>

*Presented laboratory abnormalities are listed in Table 9 below

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

Clinical relevant laboratory abnormalities are shown in Table 10.

Table 10: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>71 ≤ 3%</td>
<td>74 ≥ 3%</td>
<td>76 ≥ 3%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>59 ≤ 3%</td>
<td>61 ≥ 3%</td>
<td>63 ≥ 3%</td>
</tr>
</tbody>
</table>

*Presented laboratory abnormalities are listed in Table 10 below

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

Clinical relevant laboratory abnormalities are shown in Table 11.
and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults [see Clinical Studies (14.3) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents [see Clinical Studies (14.3, 14.4) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to ≥ 17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m² twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults. Juvenile Animal Toxicity Data Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures (e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis) occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. Geriatric Use Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with aGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Renal Impairment Total exposure of ruxolitinib and its active metabolites increased with moderate (Clcr 30 to 59 mL/min) and severe (Clcr 15 to 29 mL/min) renal impairment, and ESRD (Clcr less than 15 mL/min) on dialysis [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Modify Jakafi dosage as recommended [see Dosage and Administration (2.6) in full Prescribing Information]. Hepatic Impairment Exposure of ruxolitinib increased increased for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.
a patient that moved from California. He’s in a wheelchair from all the bortezomib he has received. I’m not saying I don’t do VRd, but I try to avoid it. [However], I don’t do CyBorD [cyclophosphamide, bortezomib, and dexamethasone] because now we have enough data—unless the patient is in renal failure, [then] yes. But cyclophosphamide is an inferior partner to bortezomib.

AMBIA: We are using 4 drugs in the high-risk category, [such as] double-hit lymphoma or the fluorescence in situ hybridization panel showing the high-risk category. Because it’s in the NCCN guidelines, it’s easy to get it authorized. Otherwise, it’s a struggle to get it authorized for standard risk.

MADAN: Is anybody else doing 4-drug inductions for high risk or standard risk?

GROVER: I have used 4 drugs as daratumumab [Darzalex] and CyBorD for myeloma associated with some amyloidosis.

MADAN: I have not used too many 4-drug regimens. I have used it, but not up front. If I do see a plateau of the response, I [will] add it. But at this point, this is something that is in flux, and practices probably will change, as well, sometime. It’s not approved, but it’s something that probably looks like it’s going to get approved soon.

**DISCUSSION QUESTION**

Which maintenance therapy do you prefer after stem cell transplant, if any?

**MADAN:** In terms of maintenance therapy, is everybody doing maintenance therapy post stem cell transplant? If yes, how many drugs? One or 2? How are we doing maintenance, and how long are we doing it for?

**KAHN:** Yes, I do maintenance after transplants. It’s usually lenalidomide, similar to what you have [in this] case.

**MUKHERJEE:** I use lenalidomide for high-risk disease [post-transplant]. I also include daratumumab if I’ve used it in the first-line setting.

**MADAN:** That’s a good point you bring, because there is a clinical trial being [planned]—it’s daratumumab/lenalidomide vs single-agent lenalidomide maintenance. That’ll be interesting.

More recently, they had data on maintenance therapy post second autologous stem cell transplant [showing] movement in the PFS. Other data came from the CASSIOPEIA trial [NCT02541383]. Patients who got daratumumab during induction don’t seem to benefit from receiving daratumumab as maintenance. We don’t have enough follow-up at this point, but that was surprising to see those patients aren’t getting a benefit. You can get benefit from either getting daratumumab in induction or getting daratumumab during maintenance therapy, [but not both]. So that was interesting.

**CASE UPDATE**

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 DVd (daratumumab, bortezomib, and dexamethasone).

One year later (2021), MRI showed new lytic lesions. The patient’s ECOG performance status was 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?”

- **CAR T-cell therapy** 43% (3)
- **Clinical trial** 29% (2)
- **Belantamab mafodotin** 14% (1)
- **Selinexor plus dexamethasone** 14% (1)
- **Second autologous stem cell transplant** 0% (0)
- **Other** 0% (0)

TOTAL VOTES: 7

CAR, chimeric antigen receptor.

**MADAN:** We have 29% [favoring] a clinical trial, which is what I would’ve gone with, and 43% going in with CAR [chimeric antigen receptor] T-cell therapy. That’s interesting. Belantamab mafodotin [Blenrep] had 14% and selinexor [Xpovio] plus dexamethasone, 14%. Who would have chosen selinexor for this patient?

**YOO:** I picked selinexor. These are good choices. Clinical trial would’ve been my answer [in practice], but if I had to pick a standard of care, selinexor is toxic but it’s...
a standard option. The patient needs to receive 4 agents [for belantamab], if I’m not mistaken. Technically, I don’t think CAR T is readily available for a standard-of-care setting. That’s why I picked a standard option.

MADAN: Selinexor plus dexamethasone is an interesting choice. When this combination was first approved, this was based on a small phase 2 trial, with a response rate of [approximately] 26%, so the drug is not bad. The problem with using selinexor plus dexamethasone is that it’s approved for twice a week, and twice-a-week selinexor therapy is not easy for somebody with an ECOG performance status of 2. You have adverse events of nausea, vomiting, hyponatremia, thrombocytopenia, fatigue, etc.

What is really impressive is what they’ve shown with STOMP [NCT02343042]. STOMP is selinexor once weekly, which is much better tolerated. It’s in combination with other therapies, such as carfilzomib and/or pomalidomide [Pomalyst]. Another trial is the BOSTON trial [NCT03110562], where selinexor once a week has been combined with bortezomib. However, based on this patient having del(17p), selinexor could be an option, because they have shown patients with del(17p) having better outcomes. Selinexor plus dexamethasone may not be the best option, but it’s still an option. You may want to combine it with something else.

NATH: This patient had a first relapse, was treated with DVd, and had a response. That is one situation when the [Center for] International Blood and Marrow Transplant Research retrospective analysis of second transplant [could be a possibility]. Do you have thoughts on a second transplant?

MADAN: I would look for at least 3 to 4 years PFS with the first stem cell transplant, which this patient has had. So this patient is right at the cusp. At least 3 to 4 years, if you compare with the data that are coming from daratumumab-based therapies in first relapse, and if you look at POLLUX [NCT02076009]. In POLLUX, the median PFS at first relapse is close to 4 years. That’s what I’m looking at. If you’re getting about 3 to 4 years from the first transplant, we’re probably going to end up getting 1 to 2 years from the second transplant. It’s never going to be the same number that you’re going to get from the first transplant. That is what you need to weigh against what you’re going to do. At least 3 to 4 years with the first transplant. A second transplant would be an option.

NATH: We can’t—or don’t want—to compare apples to oranges. When we say second transplant, I’m not saying just standard transplant, leaving, and letting the patient go. In the current age, once a patient with myeloma has progressed, you will need to have a treatment all the way through. So, [the] first time around, he had a VRd and autologous stem cell transplant, followed by lenalidomide maintenance. The second time [around], you want to do a transplant and you must up the ante of the posttransplant. Rather than maintenance, you will need a consolidation. I would argue that the daratumumab data should be following the other transplant to give him the best benefit.

MADAN: That’s fair because after the second transplant, I’ve always used maintenance with daratumumab—never with just an IMiD [immunomodulatory drug] or PI [proteasome inhibitor].

DISCUSSION QUESTIONS

- What influences your decision for the next step in this patient, who is in his second relapse?
- What is your experience with CAR T-cell therapy?

MADAN: What are [some] things you look for when you are deciding on a therapy for this patient?

MUKHERJEE: I definitely look at risk factors. If he has cardiac risk factors, I would go for carfilzomib, [as well as] prior mechanism of action. I would like to not repeat the same. If the duration of relapse is short and he’s high risk, I would discuss a second transplant or CAR T-cell therapy. The problem with CAR T-cell therapy is availability of those services in our town. I think a clinical trial at a nearby center is much more readily available than CAR T. The process of CAR T is still tedious in our state.

MADAN: Where do you refer for CAR T-cell therapy?

MUKHERJEE: Our CAR T-cell therapy is in Tennessee. It [usually] takes about 2 months for processing, screening, and time to get the patients there. So patients who have relapsed usually don’t have that much time to waste. That’s what I found with another patient who had T-cell acute leukemia. By the time I got the process—not initiated, but ongoing—he relapsed, and we had to bring him in for aggressive chemotherapy. So this is a difficulty we face at this point.

MADAN: You’re right. Has anybody else had any similar issues with referring patients to CAR T-cell therapy?

BOMGAARS: Yes, I’ve had the same issue. Out of the 5 patients I referred, there hasn’t been anybody with
myeloma who was fortunate enough to get CAR T. The only patient I have who got CAR T had diffuse large B-cell lymphoma.

NATH: The commercially available CAR T has a limited production capacity, so even locally, we have 2 centers that have it. It takes quite a long time. The other thing I want to [mention is] we have 2 CAR T therapies on clinical trial, and 1 is an off-the-shelf CAR T for patients who have had 2 prior therapies—a clinical trial certainly is available locally for [some patients].

MADAN: Absolutely. The only other thing I would add is that, regarding the clinical trials, I’ve noticed that nationally, whenever they have a slot open up, they want someone enrolled within 3 or 4 days. You either enroll or you lose it. It’s difficult to enroll in a clinical trial, even the [trial for] idecabtagene vicleucel [Abecma], because of the [production] shortage throughout the world, and it’s not activated in some locations. The CAR T is promised a lot, but it’s hard to deliver it.

MADAN: Renal impairment is very common. At least half of patients with myeloma are going to have some degree of renal impairment. How do you treat those patients? Are there any drugs you would avoid specifically? Are there any drugs you would prefer in patients with renal failure?

SHARMA: Medications like lenalidomide become a little problematic. You must look at what does not affect the immune [system as a part of] their evaluation—as far as the renal failure, too—and look for whether they have other issues or comorbidities [such as] diabetes and other things.

MADAN: We are very fortunate that most of our drugs are safe, at least in mild to moderate renal impairment. If you look at what is [available, it is] completely safe. IMiDs, except for lenalidomide, and pomalidomide are safe. Monoclonal antibodies are one of the safest drugs in renal failure, both isatuximab [Sarclisa] and daratumumab—even elotuzumab [Empliciti]—and belantamab and selinexor are also safe in these patients.

In these patients, who have had 1 to 3 prior lines of therapy, we already know it’s a very competitive space. All these drugs and their combinations, such as daratumumab, isatuximab, pomalidomide, lenalidomide-based combinations, elotuzumab, selinexor—all these are in the NCCN guidelines as category 1.3 When those patients relapse, we’re looking at patients who have progressed on an anti-CD38, a PI, and an IMiD. This opens up a whole new space.

The first drug that was approved was belantamab. That was approved in 2020. Then came the idecabtagene vicleucel. The other combination—selinexor and dexamethasone—can be used in patients who have progressed on 2 PIs, 2 IMiDs, and anti-CD38. However, I don’t think there’s too many people who would use just selinexor and dexamethasone.

DISCUSSION QUESTION

• What is your experience using belantamab?

AMBKA: Doing the Risk Evaluation and Mitigation Strategies [REMS] criteria is a pain.1 We tried giving it, and we kind of gave up.

For community practices, it’s so hard to have the staffing and enough ophthalmologists on board for weekly eye testing. REMS is the main issue. Otherwise, it’s a good medicine, at least in the current setting.

ARSLAN: The PFS [with belantamab] is 2.8 months, so why use this medication over elotuzumab or anything else?10,11 That part is not very clear. The response rates are not high. They’re approximately 30%. But if you combine it with bortezomib, there may be a better response rate. But if you use it as a single agent, the PFS is 3 months. [It doesn’t] provide much benefit in that scenario.

MADAN: I would like to clarify the eye examination is to be done once every 3 weeks, so we do it prior to starting therapy, then before each dose.9 Now the median PFS is approximately 3 months, but the median OS and the depth of response was still impressive. Remember, this was a highly refractory patient population, [with a] median of 7 prior lines of therapy.10,11

BOMGAARS: I had a patient use belantamab, and it was interesting. I thought he responded well. His light chain [and creatinine] got better. He was progressing rapidly, and I thought he was going to be on dialysis next week, then his anemia worsened to the point that he needed a transfusion. But everything got better after just 1 dose of belantamab. After the second dose, the hemoglobin went up to 9 g/dL, and the creatinine went down to 2 g. What was odd was the M protein suddenly surged up
it went to 2.9 g/dL from 2 g/dL. Initially, it was coming down from 2.5 g/dL to 2 g/dL, then suddenly it bounced right back up. I was concerned, and I talked to Mayo Clinic and asked them whether this was usual or whether this was a sign of progression? The [physician] told me it was progression, so that’s why he’s on selinexor now. But it was odd because everything was better.

**MADAN:** How many doses were you able to give him? Did he have any ocular toxicity?

**BOMGAARS:** Two. And no, he tolerated it. He was just really tired. Otherwise, he tolerated it well.

**MADAN:** That’s good. I’ve had patients on belantamab. I have 1 patient right now who’s been on this drug since April, and he’s done phenomenally well. I have another patient who was doing well, got ocular toxicity, and within a span of approximately 6 or 7 months, got belantamab maybe 3 times, and still responded. That’s exactly the data we see from this drug. [Although] the patient may not be able to get the drug, the drug is still working, so there’s still a deepening of the response in the responders. That’s important to understand. Patients are going to have ocular toxicity. You will have to hold the drug. [Unfortunately], that’s one of the things with this drug. But once the patient responds, the depth of response and the duration of response, at least on the trial, was pretty impressive—close to a year.

**BOMGAARS:** Do you know whether it [affects] the M protein, such as elotuzumab or daratumumab, at all?

**MADAN:** It is just like an IgG, but not at that level. When we detect daratumumab, [we see] very small levels in patients who are in complete remission, and suddenly we start this drug and see a small M spike or immunofixation positive, but not to the point where the M protein is going to go up from 2.2 g/dL to 2.9 g/dL. That would be very unusual.

Does anybody want to share their perception of this agent? We know it has ocular toxicity, but what else?

**GROVER:** I have not used this drug yet, so I don’t have any experience. But my main worry was—there’s 1 patient I was discussing, then she read about the ocular toxicity and was reluctant to consider. So that has been an issue with some of the patients, as well. But no, I don’t have any other concern at this time.

**AMBika:** Is there any other toxicity from payload? No interstitial lung disease or anything with this?

**MADAN:** No. If you look at the adverse event profile, it’s just the eye toxicity and thrombocytopenia. Not much of anything else.

**REFERENCES**


Arlene O. Siefker-Radtke, MD
Professor, Department of Genitourinary Medical Oncology, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

Targeted OncologyTM: What do the National Comprehensive Cancer Network (NCCN) guidelines indicate for a patient like this?

SIEFKER-RADTKE: According to the NCCN guidelines, multiple second-line treatments could be considered [for cases such as this]. The preferred regimen is pembrolizumab [Keytruda], but several other alternative preferred regimens are also listed, including erdafitinib [Balversa] and enfortumab vedotin [Padcev], and other checkpoint inhibitors, including nivolumab [Opdivo] and avelumab [Bavencio]. Other [treatment approaches include the use of] single-agent taxanes or possibly going back to chemotherapy if needed in certain situations.1

Three [immune therapy] agents are currently FDA approved [for the treatment of bladder cancer] in the second-line setting. As you may recall, there were 2 additional approvals [for this indication]: atezolizumab [Tecentriq] and durvalumab [Imfinzi]. However, these agents did not have phase 3, that is, level 1 evidence confirming [their clinical benefit in this setting], so they were voluntarily withdrawn for this indication.

Thus, we currently have 3 agents as options for the second-line treatment [of bladder cancer]. We have nivolumab, for which FDA approval was based on data from a phase 2 single-arm trial that enrolled 270 patients, showing an objective response rate [ORR] of around 20.7% and a median OS [of 8.6 months]. Adverse events [AEs] of grade 3 to 4 occurred in around 24% of patients.2,4

The other immune checkpoint inhibitors [approved for this indication] led to similar outcomes. [In 249 patients treated with] avelumab, the ORR was 17%, and the median duration of response [DOR] was similar in nivolumab [20.3 months] and avelumab [20.5 months], but a little longer with pembrolizumab [29.7 months].5

[Compared with] chemotherapy with a single-agent taxane, or vinflunine [Javelor] in Europe, [pembrolizumab led to] improvements in the ORR and overall survival [OS] and had a better toxicity profile. [These findings are considered] level 1 evidence in this setting.

So some people have asked [whether there are] differences in outcomes between these treatment groups, but these treatments appear to be similar. Variability in the patient populations and study eligibility criteria might account for observed differences between these 3 agents, all of which appear to be effective [second-line treatments for bladder cancer], but currently, the level 1 evidence favors pembrolizumab.

DISCUSSION QUESTIONS

- The patient received pembrolizumab.
- A partial response was achieved at 6 cycles.
- Molecular testing showed no FGFR2/3 mutation or fusion.

continued on page 97
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.

EXPLORE MORE POSSIBILITIES. SCAN TO VISIT TRODELVYHCP.COM.

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.

EXTRAORDINARY CLINICAL BENEFIT FOR THE TRODELVY GROUP

In the full population (n=262); 95% CI, HR: 0.43 (0.35–0.54)

In the BM-positive population (n=233); 95% CI, HR: 0.41 (0.32–0.52)

P <.0001

MEDIAN PFS

5.6 months

5.6 months

vs 6.7 months with single-agent chemotherapy (range: 10.7–14.0) (n=235) vs

6.9 months with single-agent chemotherapy (range: 5.9–7.6) (n=262);

95% CI, HR: 0.51 (0.41–0.62)

P <.0001

SURVIVAL IN TRODELVY-PLUS CASES

95% CI, HR: 0.43 (0.35–0.54)

95% CI, HR: 0.51 (0.41–0.62)

P <.0001

mTNBC
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**

<table>
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<tr>
<th>In brain metastases-negative (BM-neg) population*</th>
<th>3X LONGER MEDIAN PFS than single-agent chemotherapy</th>
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<tr>
<td>5.6 months with TRODELVY (range: 4.3–6.3) (n=235) vs 1.7 months with single-agent chemotherapy (range: 1.3–2.6) (n=233); 95% CI, HR: 0.41 (0.32–0.52) P&lt;.0001</td>
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*In the full population* | In BM-neg population* | 1 YEAR MEDIAN OS |
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<td>12.1 months with TRODELVY (range: 10.7–14.0) (n=235) vs 6.7 months with single-agent chemotherapy (range: 5.8–7.7) (n=233); 93% CI, HR: 0.48 (0.38–0.59) P&lt;.0001</td>
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*TRODELVY was studied in ASCENT, a phase 3, randomized, active-controlled, open-label trial. Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=267) or physician’s choice of single-agent chemotherapy (n=262), which included eribulin, vinorelbine, gemcitabine, or capecitabine. Patients were treated until disease progression or unacceptable toxicity. The efficacy analysis included Progression-Free Survival (PFS) in BM-neg patients (primary endpoint) by BICR based on RECIST 1.1 criteria, PFS for the full population (all patients with and without brain metastases), and Overall Survival (OS) vs single-agent chemotherapy.

- 88% of the full population were BM-neg. Results in these patients were similar to those seen in the full population (all randomized patients).

- 13% of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy). Efficacy results for this subgroup of patients were consistent with those who had received at least 2 prior lines in the metastatic setting.

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–glucuronosyltransferase 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 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.
TRODELVY® (sacituzumab govitecan-hziy) for injection, for intravenous use

INDICATIONS AND USAGE

Also see Boxed Warning, Warnings and Precautions, and Clinical Studies

TRODELVY (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated

For Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This treatment option is for patients with disease progression on or after platinum-based chemotherapy.

CONTRAINDICATIONS

Also see Warnings and Precautions

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38.

The recommended dose of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of a 21-day treatment cycle. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg. Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

TRODELVY is emetogenic. Nausea occurred in 66% of all patients treated with TRODELVY. Grade 3 vomiting occurred in 3% of patients. The most common Grade 3-4 lab abnormalities (≥25%) were neutropenia, anemia, and lymphopenia. The most common adverse reactions (≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent (>4%) adverse reactions leading to a dose reduction in 22% of patients were neutropenia, fatigue, diarrhea, nausea, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most common adverse reaction (≥25%) was neutropenia. G-CSF was used in 64% of patients who received TRODELVY.

The most common adverse reactions leading to dose interruptions in 52% of patients were neutropenia (27%, including febrile neutropenia) and nausea (25%). The most common adverse reactions leading to dose interruptions in 30% of patients were vomiting, neutropenia, and diarrhea. The most common adverse reactions leading to dose interruptions in 20% of patients were neutropenia, nausea, diarrhea, vomiting, abdominal pain, and decreased appetite. The most common adverse reactions leading to dose interruptions in 15% of patients were neutropenia, nausea, vomiting, diarrhea, abdominal pain, and decreased appetite. The most common adverse reactions leading to dose interruptions in 10% of patients were vomiting, neutropenia, diarrhea, constipation, and nausea.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity:

The incidence of Grade 3-4 neutropenia was 46% in patients homozygous for the wild-type allele (n=313). The incidence of Grade 3-4 neutropenia was 67% in patients homozygous for the UGT1A1*28 allele (n=87), 46% in patients homozygous for the wild-type allele (n=313). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients homozygous for the wild-type allele, and 11% in patients heterozygous for the wild-type allele (n=301).
How does enfortumab vedotin factor into previously treated metastatic bladder cancer?

The NCCN guidelines for postchemotherapy and post–immuno-oncology [IO] treatment list enfortumab vedotin as one of the preferred regimens, and this recommendation is due to level 1 evidence from a clinical trial. We also see that erdafitinib [is a recommended regimen in this setting] based on data from a phase 2 trial design. A variety of other regimens [are also recommended], including chemotherapy combination regimens that we have used historically, as well as, intriguingly, this new one, sacituzumab govitecan [Trodelvy].

Enfortumab vedotin received FDA approval for treatment of patients with metastatic urothelial cancer who have had prior chemotherapy and immune checkpoint inhibition therapy. The use of enfortumab vedotin [for this indication is categorized as level 1 evidence in the NCCN]. Enfortumab vedotin is a targeted chemotherapy agent that uses an antibody that targets Nectin4, a molecule commonly expressed on urothelial cancer tumors. Anywhere from 80% to 90% of patients with bladder cancer have NECTIN4 expression on their tumors, and therefore, you do not need to test for NECTIN4 expression to give this treatment.

The payload carried by the antibody is the taxane mono-methyl auristatin E, which was much too toxic to the liver as a non-targeted therapy. However, it is very effective when targeted directly to the tumor with an antibody. Once the antibody binds to the tumor cell, a protease cleavable linker releases the monomethyl auristatin E inside the tumor, resulting in cell death.

What data support this treatment?

[The phase 2 component of the] EV-201 clinical trial [NCT03474107] looked at 2 patient cohorts. Cohort 1 consisted of patients who had received prior platinum-base chemotherapy and a PD-L1 inhibitor; cohort 2 consisted of patients who had received prior treatment with a PD-L1 inhibitor but who were platinum naive. Enfortumab vedotin was given [in 28-day cycles] as a weekly dose on days 1, 8, and 15. [Accelerated approval for enfortumab vedotin] for treatment of bladder cancer in the post-platinum, post-immune checkpoint inhibitor setting was based on data from this phase 2 trial. The ORRs to enfortumab vedotin and some of these other targeted agents [were higher than any] we had previously seen in the post-frontline cisplatin setting. [In the EV-201 trial] the ORR was 44%, the median DOR was 7.6 months, and median OS was 12.4 months. The finding of a median OS of 12.4 months was remarkable in a third-line, post-chemotherapy, post-IO setting. As we all recall, historically we only achieved survival of about 1 year with front-line cisplatin-based chemotherapy. So it is truly an achievement to have the second-, third-, and additional-line treatments for urothelial cancers show such high response rates and good median OS.

In cohort 2 of the trial, which was a cisplatin-unfit cohort comprising patients who were not eligible for platinum-based therapy, the ORR was around 51%, the median duration of response was 13.8 months, and the median OS was 16 months. Some people say, “Does that mean that we should not give cisplatin?” However, these findings could just reflect of the use of additional agents or the potential for long, durable survival in this population of patients who were not eligible for standard of care-based therapy.

The phase 3 EV-301 trial evaluated the primary end point of OS following treatment with enfortumab vedotin in a post-platinum, post-checkpoint inhibitor cohort. The results [of EV-301], which were published in the New England Journal of Medicine, showed improvements in median overall survival and progression-free survival compared with single-agent taxane therapy.

What is the toxicity profile of enfortumab vedotin?

Furthermore, data from the EV-301 trial showed that enfortumab vedotin had a toxicity profile that was similar to, if not better than, a taxane, as this therapy could be used as a long-term treatment. We now have FDA approval for
enfortumab vedotin for the treatment of locally advanced or metastatic bladder cancer.

The phase 3 trial [EV-301] trial enrolled patients with urothelial cancer, including those with squamous differentiation or mixed cell types, who had evidence of radiographic progression after prior treatment with platinum-containing chemotherapy and a prior immunotherapy. Enrolled patients were randomly allocated to receive enfortumab or a single-agent taxane, as the trial evaluated several end points, the primary one being OS.

[In the trial, patients who received enfortumab had a median OS of 12.8 months]. This survival benefit is something that we had never achieved before in a third-line setting for bladder cancer and was much better than that observed in patients who received a single-agent taxane. Median survival in patients who got single-agent taxane was about 9 months, which was surprisingly long in this third-line setting. However, the trial cohort may have been enriched for patients who had benefited from prior immune checkpoint inhibition therapy.

However, toxicity is a challenge with any type of chemotherapy or targeted agent, including enfortumab. An appreciable proportion of patients who received enfortumab had AEs, including peripheral neuropathy [35%], pruritus [32%], fatigue [31%], and poor appetite [31%]. Many patients will have a poor appetite or just lose weight, which may, in part be due to a direct drug-related toxicity on the liver or the GI tract. This toxicity may induce the development of sores along the GI tract or disruption of the mucosal layer, contributing to diarrhea. When these AEs occur, withholding the drug usually results in improvement, even for peripheral neuropathy, although sometimes you have to reduce the dose or even take a break from treatment.

There are also some treatment-related AEs of special interest [for enfortumab], especially skin reactions. Nectin4 expression is found in the skin, and, thus, there is potential for skin toxicity. In animal models, the dose-limiting toxicities were diarrhea and skin reactions, such as peeling of the skin or bullous lesions of the skin. If you see a patient with peeling of the skin or bullous lesions of the skin, [which] almost look like bullous pemphigoid, that could be a sign that you are reaching a dose-limiting toxicity. So it is time to hold the therapy until the skin reaction heals and then resume treatment, if feasible. [However,] patients with skin reactions often require a dose reduction. This could be done either by dosing 2 weeks out of 3, so skipping that third weekly dose, or by reducing the dose of the therapy while maintaining the original treatment schedule of dosing 3 weeks out of 4.

There is also evidence of organ dysfunction, especially abnormal hepatic function [associated with enfortumab]. Monomethyl auristatin E is metabolized to a much higher extent in the liver than in the kidneys. [Enfortumab] monoclonal antibodies are taken up by the reticuloendothelial system and broken down in the liver, which can lead to toxic liver effects. In fact, the FDA package insert for enfortumab cautions against using this enfortumab in patients with moderate to severe liver function. So [enfortumab might not be the best therapy] for patients with a Child Pugh score of B or C.

We had a death in one of our earliest patients treated with enfortumab vedotin. This patient had a cirrhotic nodular liver and their glucose level went up [to 253 mg/dL] just before the second dose. That is why [monitoring glucose levels is] recommended for patients receiving enfortumab.

**Are there any scenarios where treatment needs to be adjusted?**

[Enfortumab therapy] should be withheld in a patient whose glucose is above 250 mg/dL because this could be a dose-limiting toxicity. The patient who passed away had a glucose level just barely above [250 mg/dL], but this individual was not diabetic. Notably this patient also experienced diarrhea and developed bullous [skin lesions] and peeling skin, a presentation that made some of us wonder if this could be Stevens-Johnson syndrome. I think that high doses and off-target drug activity introduced the drug into the skin, resulting in disruption of the skin. So be cautious in patients with cirrhotic livers; [even in patients with] mild to moderate liver dysfunction you should consider starting treatment at a reduced dose.

One of the benefits of [enfortumab] is that it is not associated with myelosuppression, and, therefore, you do not need to use as much growth factor support in [patients who receive] this therapy. I have yet to use growth factor [in this setting], so enfortumab is easier on the bone marrow and works particularly well in patients with bone metastases.

I have been very impressed by the sclerotic changes in the bone [that occur in some patients who receive enfortumab]. If a patient has sclerotic changes and bone pain is improved, that is a sign of treatment response. Sometimes, [as part of this treatment response,] the bone scan will show increased interval activity due to an osteoblastic reaction, resulting in the sclerotic lesions.

**Are there other therapies to consider for a patient like this?**

Sacituzumab govitecan is another novel antibody-drug conjugate therapy that works by delivering a toxic payload of irinotecan directly into the tumor, thereby minimizing [drug-related] toxicity. [Sacituzumab govitecan’s] high drug-to-antibody ratio enables a high concentration of payload to be directed into the cancer cell, where it is released through hydrolysis. Sacituzumab govitecan’s antibody is directed toward Trop-2 expression, which is present in about 80% of urothelial carcinoma tumors. Given this high prevalence
of expression, testing for Trop-2 expression is not required before using sacituzumab govitecan.

Sacituzumab govitecan has significant activity across multiple tumor types and is already approved for the treatment of patients with breast cancer. [Furthermore, this agent] has a very good toxicity profile and in a phase 2 trial, patients with metastatic epithelial cancer treated with sacituzumab govitecan had an ORR of around 30%, a median progression-free survival of 7.3 months, and a median OS of 16.3 months. [Based on these data, sacituzumab govitecan] received accelerated approval for triple-negative breast cancer and fast track designation for urothelial cancer, and a phase 3 trial of sacituzumab govitecan treatment for urothelial cancer is ongoing.

**POLLING QUESTION**
At a live, virtual event, Siefker-Radtke asked participants, “How likely are you to use sacituzumab govitecan for your patients with advanced metastatic urothelial cancer [mUC]?”

- Likely 56% (5)
- Very likely 33% (3)
- I am currently using sacituzumab govitecan for advanced mUC. 11% (1)
- Neutral 0% (0)
- Unlikely 0% (0)
- Very Unlikely 0% (0)

TOTAL VOTES: 9

**What data support the use of sacituzumab govitecan?**
The [phase 2, two-arm] TROPHY-U-01 trial [NCT03547973] included a cohort composed of 100 patients with metastatic urothelial cancer who had progressed following platinum-based therapy and checkpoint inhibitor therapy. [At the time this trial was undertaken] accelerated approval for enfortumab had been granted, so standard-of-care therapies might have included enfortumab as well as erdafitinib.

Sacituzumab govitecan was given to patients at a dose of 10 mg/kg on days 1 and 8 of each 21-day cycle. Dosing sacituzumab govitecan on a 3-week schedule, in this way, improved its tolerability, enabling continued treatment for many months to achieve durable activity and responses [as have been seen for enfortumab vedotin]. So if the patients were benefiting and not having significant toxicity, they continued this therapy.

The primary end point of TROPHY-U-01 was the objective response rate as assessed by central review; secondary end points were duration of response, PFS, and OS. [Trial patients tended to be older]; 23% were over the age of 75 and heavily pretreated, and the median number of prior anticancer regimens was 3. [Commonly used] prior therapies included carboplatin and cisplatin and, in total, 72% of patients had an [ECOG] performance status of 1.

[However,] I have heard oncologists argue that when you are enrolling patients with a performance status of 1, you are probably getting those with a performance status of 2 because we are so eager to find novel therapies for these patients. [In total, 62% of the trial patients had] visceral metastases, including 28% with liver metastases and those typically have a poor prognosis even with immune checkpoint inhibitor treatment in the second-line setting. The Bellmunt risk score indicates that many trial patients had multiple risk factors, which indicates a poor prognostic.

The ORR for patients was 31%, [which I think is a very good response rate in this heavily pretreated patient cohort].

Some have said, “Well, this is lower than [the response rate for] enfortumab vedotin.” It is numerically lower, but it is not a head-to-head comparison. The lower response rate may reflect the heavily pretreated nature of the TROPHY-U-01 cohort, which may have included many patients with prior erdafitinib or enfortumab treatment. The trial’s complete response rate was around 5%, the partial response rate was around 22%, and the median DOR was 7.2 months. Median OS in the trial was 10.9 months, which is truly remarkable [in this heavily pretreated cohort]. Keep in mind that in trials of frontline carboplatin therapy for metastatic disease, carboplatin did not always achieve a median survival of 10.9 months.

**What is the toxicity profile for sacituzumab govitecan?**
Sacituzumab govitecan has toxicity, and good management of that toxicity can help keep patients on treatment longer. [Sacituzumab govitecan] has a different toxicity profile from that of enfortumab vedotin but is not associated with neuropathy, so it could be a good option for patients who have preexisting neuropathy and cannot tolerate taxane-based therapy. [However, sacituzumab govitecan] can lead to neutropenia, which was seen in 46% of patients, including 34% of grade 3 or 4.

Trial patients experienced other AEs of grade 3 or 4, including anemia [14%], leukopenia [17%], lymphopenia [7%], and neutropenic fevers [10%]. Diarrhea was also a common AE in trial patients; however, the diarrhea was a little different from that associated with enfortumab vedotin. [In patients treated with enfortumab vedotin], diarrhea typically occurs toward the end of the cycle and is a sign of mucosal toxicity, whereas with sacituzumab, it can occur on the day of or the day following the infusion. I think this is because irinotecan can induce diarrhea as well as decreased appetite and hair loss.
Roundtable Discussion: Kuzel Walks Through New Treatment Options in Advanced RCC

CASE SUMMARY

A 59-year-old Black woman received a diagnosis of stage IV clear cell renal cell carcinoma (RCC). She underwent a left total nephrectomy in December 2019. Nine months later, she developed metastatic disease to bilateral lung, mediastinum (35 × 38 mm), and retroperitoneal lymph nodes. Her Karnofsky performance status score was 90%. Her hemoglobin, neutrophils, and platelets were within normal limits. Her elevated corrected calcium was above the upper limit of normal. The patient received pembrolizumab (Keytruda) plus lenvatinib (Lenvima) as part of a clinical trial treatment.

DISCUSSION QUESTIONS

• How do you assess patient risk?
• Does risk status influence your frontline decision-making for a patient such as this?
• What additional work-up do you typically order?
• Would you initiate systemic therapy at this point?

KUZEL: How do [clinicians] assess patient risk nowadays? Do you go through the steps involved [for calculating the IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) risk score]? Or use any of the various algorithms? Or do we just sort of look at the stage and leave it at that?

GUNDALA: Yes, we do look at the score. And we take into consideration all the risk factors that are mentioned on the [IMDC] risk calculator: the duration from the surgery to reoccurrence, patient performance status, and all the laboratory values—calcium, hemoglobin. That helps you separate the patients [with] intermediate or poor prognosis vs favorable [prognosis].

KUZEL: [The IMDC] has been updated recently, so once you make that decision, do you use different therapies for favorable, intermediate, poor [prognoses]? Or at this point does it matter?

GUNDALA: We have so many options that I don’t know if there is a slight difference between them, between the favorable and less favorable [prognoses]. Because we can use the pembrolizumab immunotherapy combination with lenvatinib [or axitinib (Inlyta)]. Of course, we have the doublet immunotherapy, but I’m not clear if there is one better than the other, besides the data that I know about nivolumab [Opdivo] plus ipilimumab [Yervoy].

SHAH: I do have a couple of patients in later lines of therapy [who have] failed all other therapies and appreciate your option always. And I think there is something special about… nivolumab plus ipilimumab and I’ve had patients [with intermediate and favorable, intermediate, poor [prognoses]]...
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.
Fractures of the femur, hip or acetabulum were reported in patients followed per fracture.

Among 187 adult patients who received VITRAKVI, increased AST leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. The median time to onset of increased AST was 2.1 months (range: 1 day to 4.3 years). The median time to onset of increased ALT was 2.1 months (range: 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). 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 4.3 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.

### Important Safety Information (continued)

#### Central Nervous System Effects (continued):
Mood disorders occurred in 14% of patients. The median time to onset of mood disorders was 3.9 months (range: 1 day to 40.5 months). Mood disorders occurring in ≥1% of patients included anxiety (5%), depression (3.9%), agitation (2.9%), and irritability (2.9%). Grade 3 mood disorders occurred in 0.4% of patients. Dizziness occurred in 27% of patients, and Grade 3 dizziness occurred in 1.1% of patients. Among the 74 patients who experienced dizziness, 5% of patients required a dose modification and 5% required dose interruption.

Sleep disturbances occurred in 10% of patients. Sleep disturbances included insomnia (7%), somnolence (2.5%), and sleep disorder (0.4%). There were no Grade 3-4 sleep disturbances. Among the 28 patients who experienced sleep disturbances, 1 patient each (3.6%) required a dose modification or dose interruption.

Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

**Skeletal Fractures:** Among 187 adult patients who received VITRAKVI across clinical trials, fractures were reported in 7% and among 92 pediatric patients, fractures were reported in 9% (N=279; 8%). Median time to fracture was 11.6 months (range 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). 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 4.3 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.

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* VITRAKVI® is indicated for the treatment of adult and pediatric patients with NTRK gene fusion-positive solid tumors. 
* The most common adverse reactions included abdominal pain (21%), vomiting (25%), pyrexia (24%), lymphopenia (22%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (34%), cough (32%), leukopenia (28%), constipation (27%), arthralgia (36%), neutropenia (36%), increased alkaline phosphatase (25%), proteinuria (25%), and edema (25%).
* Important Safety Information: Rare cases of serious heart valve disorders have been reported in patients treated with VITRAKVI. These heart valve disorders may be irreversible.
* Lactation: Advise women not to breastfeed during treatment with VITRAKVI.
* Co-administration: Avoid co-administration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John's wort), and sensitive CYP3A4 substrates. If co-administration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify or withhold VITRAKVI dosage as recommended. If co-administration of strong CYP3A4 inhibitors cannot be avoided, monitor for increased adverse reactions of these drugs.
* CYP3A4: CYP3A4 is involved in the metabolism of VITRAKVI.
* Pregnancy: Treatment with VITRAKVI may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. VITRAKVI may cause fetal harm when administered to a pregnant woman. It is unknown if VITRAKVI is excreted in human milk. Advise pregnant women of the potential for a fetal hazard; advise women of reproductive potential to use effective contraception during and for at least 4 weeks after therapy; advise breastfeeding women not to breastfeed during treatment with VITRAKVI.

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**Find the Oncogenic Driver Early and Act with VITRAKVI Where it Starts**

**The #1 prescribed TRK inhibitor for NTRK gene fusion-positive solid tumors**

Across solid tumors

**FUSION POSITIVE.**

**POSITIVE RESULTS.**

**FUSION POSITIVE.**

**POSITIVE RESULTS.**

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*A NTRK: neurotrophic receptor tyrosine kinase; TRK: tropomysosin receptor kinase.
Based on medical claims and prescription data claims for the period August 2019 through December 2020. Validated by IQVIA in March 2021.**
**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**
  - (n=14/55)
  - **1 in 4 patients had a complete response**

- **49% PR**
  - (n=27/55)

- **75% ORR**
  - (95% CI: 61%, 85%)
  - (n=41/55)

*CR, complete response; ORR, overall response rate; PR, partial response.*

**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>c</sup>Kaplan-Meier estimate.
*<sup>b</sup>denotes ongoing response.

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

**TEST. TRK. TREAT.**

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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.

**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.

**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%), hypoalbuminemia (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.

**Visit VITRAKVI.com**

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**References:**

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BRIEF SUMMARY OF PRESCRIBING INFORMATION PAGE 200 FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

• harbor 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 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.

2 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, and seizures.

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 5.1 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 23% required dose interruption.

Mood disorders occurred in 14% of patients. The median time to onset of mood disorders was 3.9 months (range: 1 day to 40.5 months). Mood disorders occurring in ≥ 1% of patients included anxiety (5%), depression (3.9%), agitation (2.9%), and irritability (2.9%). Grade 3 mood disorders occurred in 1% of patients. Dizziness occurred in 27% of patients, and Grade 3 dizziness occurred in 1.1% of patients. Among the 74 patients who experienced dizziness, 5% of patients required a dose modification, and 5% required dose interruption.

Sleep disturbances occurred in 10% of patients. Sleep disturbances included insomnia (7%), somnolence (2.5%), and sleep disorder (0.4%). There were no Grade 3-4 sleep disturbances. Among the 28 patients who experienced sleep disturbances, 1 patient each (3.6%) required a dose modification or dose interruption.

Advise patients and caregivers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurocognitive adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed [see Dosage and Administration (2.3)].

5.2 Skeletal Fractures

Among 187 adult patients who received VITRAKVI across clinical trials, fractures were reported in 7% and among 92 pediatric patients, fractures were reported in 9% (N=279; 8%). Median time to fracture was 11.8 months (range 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). 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.

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%. Grade 3-4 increased ALT of any grade occurred in 2.5% of patients, respectively (see Adverse Reactions [6.1]). The median time to onset of increased AST was 1.6 months (range: 0.3 to 4.3 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 every 4 to 8 weeks. If an increased AST or ALT occurs, withhold VITRAKVI, and modify the VITRAKVI dosage when resumed if the ALT or AST is ≤ 2.5 times the upper limit of normal (ULN). If the ALT or AST remains greater than 5 times the ULN, VITRAKVI should be discontinued.

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

5.4 Embryo-Fetal Toxicity

The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from across these 279 patients, the median age was 46 years (range: 0.1 days to 84 years); 33% were younger than 18 years. 48% were male, and 74% were White, 9% were Hispanic/Latino, 7% were Asian and 6% were Black. The most common tumors (35%) in order of decreasing frequency were soft tissue sarcoma (14%), thyroid (13%), intestinal (12%), primary central nervous system (CNS) (11%), salivary gland (9%), lung (9%), colon (8%), breast (4%), or melanoma (3%).

VITRAKVI and other proteolysis were confirmed or inferred in 75% of VITRAKVI-treated patients. Most adults (86%) received VITRAKVI 100 mg orally twice daily and 85% of pediatric (<18 years) received VITRAKVI 100 mg/m² twice daily up to a maximum dose of 100 mg twice daily. The dose was reduced from 50 mg daily to 200 mg twice daily in patients with CrCl < 30 ml/min and 3.6 mg/m² twice daily to 120 mg/m² twice daily in pediatrics [see Use in Specific Populations (8.4)].

The most common adverse reactions (≥ 20%), including laboratory abnormalities, in order of decreasing frequency, were increased AST, increased ALT, increased alkaline phosphatase, increased ALT and AST, increased gamma-glutamyltransferase, hypoaalbuminemia, neutropenia, increased alkaline phosphatase, cough, leukopenia, constipation, diarrhea, dizziness, hypocalcemia, nausea, vomiting, pyrexia, lymphopenia, and abdominal pain.

The most common serious adverse reactions (≥ 2%) were pneumonia, and pyrexia. Grade 3 or 4 adverse reactions occurred in 53% of patients; adverse reactions leading to dose interruption or modification occurred in 39% and 8% of patients, respectively, and 9% permanently discontinued VITRAKVI for adverse reactions.

The most common adverse reactions (1%) each that resulted in permanent discontinuation of VITRAKVI were increased ALT, increased AST, dehydration and fatigue.

The most common adverse reactions (≥ 2%) resulting in dose interruption were increased ALT (4.7%), increased AST (4.3%), and neutrophil count decreased (4.3%). Most (10%) adverse reactions leading to dose interruption occurred during the first three months of exposure.

Adverse reactions of VITRAKVI occurring in ≥ 10% of patients and laboratory abnormalities worsening from baseline in ≥ 20% of patients are summarized in Table 2 and Table 3, respectively.

Table 2 Adverse Reactions Occurring in ≥ 10% of Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Adverse Reaction*</th>
<th>VITRAKVI N = 279</th>
<th>All Grades***</th>
<th>Grade 3-4***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>42</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>10</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td>17</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>38</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>19</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Medastinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>32</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>17</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>11</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness*</td>
<td>27</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Cognitive Impairment*</td>
<td>11</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>27</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>19</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood disorders*</td>
<td>14</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Sleep Disturbance*</td>
<td>10</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>14</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection*</td>
<td>12</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

*The adverse reaction identifies a composite term:

†Includes: arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

‡Includes: fatigue, anemia, generalized edema, lip edema, localized edema, edema, edema genital, edema peripheral, periorbital edema, and swelling.

§Includes: cough, productive cough, and upper-airway cough syndrome.

∥Includes: dyspnea, and dyspnea exertional.

¶Includes: dizziness, dizziness postural, and vertigo.

‖Includes: asthenia, apathia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, memory impairment, mental impairment, mental status changes.

¶¶Includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.

††Includes: dermatitis, dermatitis acnioform, dermatitis bullos, dermatitis exfoliative generalized, eczema, eczema astetic, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash maculopapular, rash papular, rash pruritic, and rash pustular.

‡‡Includes: agitation, anxiety, depression, depressed mood, euphoric mood, irritability, mania, mood change.

§§Includes: cystitis, escherichia urinary tract infection, pyelonephritis acute, and urinary tract infection.

**National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.

Clinical relevant adverse reactions occurring in ≥ 10% of patients include fractures (8%).
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 trials 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 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 infundibuloma (31%), primary CNS tumors (28%), and rhabdomyosarcoma (7%).

Table 3 Laboratory Abnormalities Occurring in ≥ 20% Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>52</td>
<td>3.1</td>
</tr>
<tr>
<td>Decreased AST</td>
<td>45</td>
<td>2.5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22</td>
<td>8</td>
</tr>
</tbody>
</table>

Based on NCI CTCAE v4.03

**Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 272 to 277 patients.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VITRAKVI

Co-administration of VITRAKVI with a strong CYP3A4 inducer may increase larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If coadministration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended [see Dose and Administration (2.4)].

7.2 Effects of VITRAKVI on Other Drugs

Skin toxicity and related adverse reactions

7.3 Laboratory Assessment

Co-administration of VITRAKVI with a strong CYP3A4 inducer may decrease larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI [see Clinical Pharmacology (12.3)]. Avoid coadministration of VITRAKVI with strong CYP3A4 inducers, including St. John’s wort. If coadministration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Dose and Administration (2.5)].

7.4 Use in Specific Populations

8 Pregnancy

8.1 Pregnancy Risk Category

Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily (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 25%, respectively.

Data

Human Data

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Animal Data

Larotrectinib crosses the placenta in animals. Larotrectinib did not result in embryolethality at maternally toxic doses; [up to 40 times the human exposure based on area under the curve (AUC) at the clinical dose of 100 mg twice daily] in embryo-fetal development studies in pregnant rats dosed during the period of organogenesis; however, larotrectinib was associated with fetal anasarca in rats from a study in which the maternal exposure at twice-daily doses of 40 mg/kg [11 times the human exposure (AUC) at the clinical dose of 100 mg twice daily]. In pregnant rabbits, larotrectinib administration was associated with omphalocoele and pyloric stenosis at twice-daily doses of 15 mg/kg (0.7 times the human exposure at the clinical dose of 100 mg twice daily).

8.2 Lactation

Risk Summary

There are no data on the presence of larotrectinib or its metabolites in human milk and no data on its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with larotrectinib and for 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

8.3.1 Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating VITRAKVI [see Use in Specific Populations (8.4)].

Controlled Maternal-Offspring Exposures

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

Females

Advise female patients of reproductive potential to use effective contraception during treatment with VITRAKVI and for at least 1 week after the final dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with VITRAKVI and for 1 week after the final dose.

8.4 Pediatric Use

There is limited information from the reproductive tracts of female rats in a 1-month repeated-dose study. VITRAKVI may reduce fertility [see Nonclinical Toxicology (13.1)].

8.5 Geriatric Use

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A). Larotrectinib clearance was reduced in subjects with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.1)]. Reduce VITRAKVI dose as recommended [see Dose and Administration (2.6)].

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with renal impairment of any severity [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

17.1 Advise patients that they will need to undergo laboratory tests to monitor liver function [see Warnings and Precautions (5.3)].

17.2 Embryo-Fetal Toxicity

Advisement patients and their families of the potential risk to the fetus [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)].

Advisement to females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective contraception during the treatment with VITRAKVI and for at least 1 week after the final dose. [see Use in Specific Populations (8.2)].

Advisement to males with female partners of reproductive potential to use effective contraception during treatment with VITRAKVI and for at least 1 week after the final dose. [see Use in Specific Populations (8.1)].

17.3 Infertility

Advise females of reproductive potential that VITRAKVI may impair fertility [see Nonclinical Toxicology (13.1)].

17.4 Drug Interactions

Advisement patients and caregivers to inform their healthcare provider of all coadministered medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit or grapefruit juice while taking VITRAKVI [see Drug Interactions (7.1, 7.2)].

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poor risk] respond to that combination....I think [for patients at] intermediate or poor risk I’m still using nivolumab plus ipilimumab. Favorable risk, certainly pembrolizumab plus lenvatinib or pembrolizumab plus axitinib is reasonable.

SHEKHANI: The rationale for separating intermediate vs low risk vs high risk is because you can choose a treatment based on the risk....You don’t want to use high-risk medications for low-risk patients who can benefit from a single-agent pazopanib [Votrient] or some “nib,” rather than combination immunotherapy.

They do carry high risk, so I personally separate them out based on the risk factors. Just so that I can choose and appropriately [assess the] risk [of the] treatment for the disease that I’m dealing with.

KUZEL: I’m glad you mentioned some of that. At least some of you still are using single-agent, tyrosine kinase inhibitors [TKIs]? You don’t automatically default to one of the doublets?

SHEKHANI: Not in a low-risk patient, not in a high comorbid patient, not in an elderly patient with high risk, or a patient with autoimmune disease. I would prefer to use a single-agent “nib.” [And not] if the patient is at low risk and if the treatment carries a higher risk than the disease itself does.

SHULMAN: If they have very slow-growing disease, I’ve just done a single agent as Dr Shekani mentioned—just as a trial to see how they would do with that before putting them on 2 different drugs. If they have very small, indolent disease...or as in this case with the calcium being marginally elevated, it might make me a little more nervous about observing them.

KUZEL: Does anybody have experience with lenvatinib in any setting either with everolimus [Afinitor] or pembrolizumab? Does anybody use that for their relapsed-refractory patients?

TAJUDDIN: I’ve used it in [treating patients with] thyroid cancer.

KUZEL: OK, so you have lenvatinib experience in a different disease, but at least you have that experience. That’s the beauty of talking to [clinicians] who do a little bit of everything. They may have used some of these drugs in other disease settings. Has anyone ever used it in kidney cancer with everolimus?

GUNDALA: Yes, I did use it.

KUZEL: What did you think?

GUNDALA: It wasn’t easy. [For] the stomatitis we needed the dexamethasone and we knew what to do about that, but the hypertension and edema, proteinuria, asthenia, those are difficult issues that we needed to dose down the patient. [The patient] did respond, he had a significant response and duration of response, but it was not easy in terms of quality of life and [adverse] effects.

KUZEL: Which drugs did you blame for the toxicities mostly?

GUNDALA: I think initially I dosed down the everolimus. And then subsequently I had to dose down the lenvatinib, I think, because the edema was getting worse.

KUZEL: Nobody has used it with pembrolizumab, I’m guessing.

SHEKHANI: I am currently using [it] on 1 patient, pembrolizumab with lenvatinib for anaplastic thyroid carcinoma. It’s based on a single study—it’s a phase 1, early phase 2 [trial] from [The University of Texas MD Anderson Cancer Center in Houston]. And after discussing with MD Anderson, we decided to try that. Luckily we were able to get approval as well. And so far the patient has been tolerating it fairly well. But it’s a combination for anaplastic thyroid.

KUZEL: Right. But, at least in terms of the combination, you haven’t run into any unusual toxicities that would have made it easier or more difficult to treat?

SHEKHANI: No, in this particular patient, I am finding lenvatinib to be better tolerated than I found in a younger man with metastatic thyroid carcinoma when it was single agent, and I had a difficult time getting that one in that [patient]. So I was just dreading it, [worrying] that it was going to be a problem, especially with the pembrolizumab diarrhea, the lenvatinib diarrhea, the stomatitis, and all those things. But this patient has done amazingly well.

**Polling Question**

“A decision was made to initiate systemic therapy. What frontline therapy are you most likely to choose for this patient?”

<table>
<thead>
<tr>
<th>Therapy Combination</th>
<th>Percentage</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib plus pembrolizumab</td>
<td>43% (3)</td>
<td></td>
</tr>
<tr>
<td>Nivolumab plus ipilimumab</td>
<td>29% (2)</td>
<td></td>
</tr>
<tr>
<td>Cabozantinib plus nivolumab</td>
<td>14% (1)</td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>14% (1)</td>
<td></td>
</tr>
<tr>
<td>Lenvatinib plus pembrolizumab</td>
<td>0% (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0% (0)</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL VOTES:** 7

KUZEL: Does anybody have experience with lenvatinib in any setting either with everolimus [Afinitor] or pembrolizumab? Does anybody use that for their relapsed-refractory patients?
KUZEL: What do you think of the CLEAR [NCT02811861] data?¹

SHULMAN: I think one thing that struck me is there’s a big difference in progression-free survival between the pembrolizumab plus lenvatinib [group] vs [the group receiving] sunitinib [Sutent].¹ But the survival data, and again it’s a shorter follow-up, but the curves kind of come together and you might have a more effective combination inducing a response or shrinking disease. But then you wonder if you look at the composite of complete or partial response, or stable disease if they are more similar in that vein.

DISCUSSION QUESTIONS
• How will use of this combination in the front line affect your second-line decision-making?
• How will you counsel patients regarding this regimen?
• What is your impression of its safety/tolerability?
• Are you familiar with the recommended dosages?

KUZEL: So, do you think about second-line or-third line therapy when you’re making a choice for first-line treatment? Or do you avoid a drug that would be in a combination in the frontline setting because you want to use it in the second-line setting?

TAJUDDIN: I think with advanced and high-risk metastatic disease you have the window of opportunity to treat ahead the first time. You might never get a second opportunity, so might as well use the best you have.

SHEKHANI: Same here—first try to give it your best shot. You don’t know if you’re going to have a good enough performance status to go with a more aggressive second line or not. [Also,] with the precision medicine you can identify some of those medications based on that as well.

So it’s not necessarily going to be less “pick from the basket” and see which one comes out. It’s [determined by whether] the precision medicine gives you some idea to target on either first line or second line.

SHEKHANI: I did 14 mg, 20 mg, and 24 mg. I think 24 mg is the highest one that’s been used in any trial—any single agent as well. But 12 mg and 14 mg are probably [used often]; 14 mg I think is the one they use more commonly.

KUZEL: Lenvatinib at 18 mg and 5 mg of the everolimus are the starting doses.²³ In the CLEAR trail, the lenvatinib with pembrolizumab is actually 20 mg.¹

TAJUDDIN: For thyroid [cancer], the recommendations are the escalating doses of lenvatinib. Is something such as that useful here?

KUZEL: You know, that’s an interesting question. There are [clinicians] who have been proponents that for some of these toxic combinations maybe we should start lower, and if they tolerate it, escalate. Then, there are others who feel that if you do that you don’t get a response; you’re going to bail out when it had just started at the higher dose.

So with lenvatinib, which I tend to use it in salvage, sometimes I don’t start at 18 mg because I just know based on prior TKI experiences with that patient they will never tolerate 18 mg. So I’ll purposely start lower, but with lenvatinib plus pembrolizumab in the frontline setting, I don’t think starting low makes a lot of sense. I think you go with full dose and deescalate if the patient doesn’t tolerate it and I think that makes the most sense in the frontline setting.

The dosing of lenvatinib is 20 mg daily, and the pembrolizumab was given every 3 weeks. I’m sure many of us probably would give it every 6 weeks, but in the trial it was given every 3 weeks [at] the older dosing.¹ And the pembrolizumab was given for 2 years. At the end of 2 years investigators were allowed to continue lenvatinib as a single agent for as long as the patient tolerated it, or [until] the patient progressed, or [if] the patient just stopped wanting to take it. So that’s a little bit different than some of the combinations where you might give it for just 2 years.

The dose forms of lenvatinib, which I mentioned, are either 4-mg or 10-mg capsules.² When you start with lenvatinib it’s 18 mg, so it’s a 10-mg capsule and 2 of the 4-mg capsules. In this case you start with two 10 mg capsules, so the next dose reduction down is the 14-mg dose. That’s your sort of deescalation scale. I’ve never given anybody 8 mg but I dose reduced a lot of patients down to 10 mg with that drug.

DISCUSSION QUESTIONS
• What are your reactions to the CheckMate 9ER (NCT03141177) data?
• How will you counsel patients regarding this regimen?
• What is your impression of its safety/tolerability?
• Are you familiar with the recommended dosages?
• How would use of this combination in the frontline affect your second-line decision-making?

KUZEL: Do you like this CheckMate 9ER regimen [of nivolumab plus cabozantinib (Cabometyx)]?¹ Have you tried this? Has anybody used it in the salvage setting?
SUH: I’ve used this regimen in a few patients with metastatic disease. And the reason I chose it is that I have some experience with cabozantinib and with immunotherapies. [It is] well tolerated so I felt comfortable doing this combination.

KUZEL: Are there certain patients that you would skew toward this regimen over pembrolizumab plus axitinib? You have 2 patients sitting in your office. Would you look at [one of them] and say I’m going to do cabozantinib plus nivolumab for this one for some reason?

SUH: For my patients they were both intermediate for risk. Because of the more recency of the data, I wanted to gain more experience in using this regimen.

KUZEL: If a patient has bone metastases, does that factor into anybody’s thinking? You might say, “I heard something about bone metastases with cabozantinib, maybe I’ll give nivolumab plus cabozantinib a try.” Or hasn’t that penetrated?

SHULMAN: I just heard that bone metastases are difficult with immunotherapy but it wasn’t that cabozantinib was better.

KUZEL: Would you even give a combination? Or would you shy away from a combination?

SHULMAN: Well, it seems from what you’re saying that you don’t know if there’s synergy. With cabozantinib plus nivolumab, it may add something to the cabozantinib.

KUZEL: So do you think that these are just additive combinations?

SHULMAN: I think the response rates indicate maybe there’s some synergy and it seems [as though] the progression-free survival may be additive, but it seems you’re getting a lot more response than you would with sequential therapy.

DISCUSSION QUESTIONS

- How do you assist/discuss patients’ financial toxicity?
- What are the most helpful resources to you, your practice, and your patients in this regard?
- How would you counsel patients regarding this regimen?

KUZEL: Is the goal when we treat these patients to just extend progression-free survival by a few months? Or is cure what we’re shooting for? When you counsel a patient with kidney cancer, what do you tell them?

SHULMAN: Unless they’re getting high-dose IL-2, I try to give them the best response, with the best quality of life, and help them live the longest. In general their disease is not going to be—hate to use the word cure—not curable, but that’s kind of how I say it. It’s not as though you’re going to die from it, but we can’t cure it.

KUZEL: I use the C word [cure], and I certainly use it with ipilimumab plus nivolumab and I think the justification for these is similar. The TKI is supposed to make the nivolumab work better or the pembrolizumab work better, so it’s not necessarily just additive; hopefully it is synergistic.

And it’s the tail on the curve that we’re obviously all interested in and with only 2-, 3-, 4-year follow-up, we’ve done so well that all the patients are still alive. We haven’t even reached the median survival yet. I think it will be interesting to see if there’s a tail on that curve with these combinations. I think hopefully there will be.

TAJUDDIN: So those who survive longer, is that the nature of the disease that they have? That’s why they’re surviving longer? Or is it just their therapeutic interventions that are changing and [helping] them live longer?

KUZEL: Well, that’s why the risk group stratification is important, I think, and the makeup of the trials is important. We know that intermediate- or poor-risk patients have actually relatively short survival. I mean, they have disease and [those with] favorable risk have a long survival. When you put a lot of favorable-risk patients [in a trial] it clouds that picture, but intermediate- and poor-risk patients don’t do very well. I think that if you can [affect] the natural history on intermediate- and poor-risk patients, it’s treatment related.

[I had a patient where] we took his lung mass out and everything went away, spontaneous remission. It is always hard because they were always so infrequent, but with these regimens the response rates are very high and hopefully durable.

KUHL: Does anybody think that the tolerability of the nivolumab plus cabozantinib looks better than their pembrolizumab plus axitinib experience? Or better than the lenvatinib plus everolimus or the lenvatinib plus pembrolizumab data? Was there a toxicity reason to choose maybe one of these regimens [over another]?

SUH: I found the lenvatinib is quite difficult for patients to tolerate, I’ve used it in patients with thyroid cancer.
There are a lot of issues with weight loss, anorexia, and gastrointestinal toxicities. I prefer cabozantinib over lenvatinib.

KUZEL: So the TKI toxicity does help you choose your regimen. Do you like to use axitinib? I mean, nobody used to like using sunitinib. Is axitinib a preferred TKI? Do you find you’re comfortable with that in terms of managing toxicities?

SHEKHANI: [There are] no data, but I would prefer poziotinib, over axitinib in time. Because I think my experience with poziotinib has always been the best. But axitinib is OK. Unfortunately, hypertension has been a problem, cardiac issues have been a problem [for] those patients on axitinib.

KUZEL: Of course, single-agent cabozantinib has been a choice in this group of patients. [In terms of doses of] 60 mg of cabozantinib vs 40 mg of cabozantinib, do you find a big difference? Or do most [clinicians] start at 40 mg when they’re using a single agent of cabozantinib?

SHEKHANI: [Yes] 40 mg, I could count the number of patients on my fingertips who have been able to tolerate 60 mg. The 40 mg has been better. The 20 mg—most of them are usually able to do that.

KUZEL: You don’t start at 60 mg and rapidly dose reduce? You have given up on 60 mg?

SHEKHANI: [It] depends on who’s on call on the weekend when I first start. If I’m on call, I’m starting [at] 40 mg.

KUZEL: [If you have] patients sitting in front of you, is there any clinical feature of a patient that makes you choose one regimen over the other? Or are most of you [using a] favorite regimen and you’re going to stick with it most of the time?

SHEKHANI: For me, if it’s mostly bone lesions, I prefer not to have dual immunotherapy or try to have at least one of the “nibs”. But, if it’s a visceral disease, and I need a quick response, and there’s no other comorbidities or anything like that, I may go for combination immunotherapy.

KUZEL: OK, what about brain metastases? Do they factor in at all when you’re thinking about these regimens?

SHEKHANI: For the brain metastases I prefer to have an immunotherapy, especially combination if the brain metastases are more [of a] priority than any visceral involvement.

KUZEL: Who helps you manage toxicities? Does everybody have nurse practitioners, physician assistants who chip in? PharmDs who work with you? Or does it all just roll back to you?

SHULMAN: Rolls back to us usually. At least in my case.

KUZEL: Things were slightly better before the COVID-19 cost-cutting era. But since then it’s been mostly [up] to us.

KUZEL: Is that just because you don’t have enough staff [due to the pandemic]?

SHEKHANI: [Many of] the staff have been let go by the administration and the cost-cutting has been everywhere, I’m sure. Certainly it just falls back on the physician eventually.

KUZEL: [Is there] anybody else who takes calls that specifically deal with toxicity? I always marvel that at [Memorial Sloan Kettering Cancer Center in New York, New York], they had a [dedicated] adverse event, immunotherapy inpatient service....Does anybody have something [similar to] that at their institution or organizations? Is there somebody in the practice who specializes in that? Or it’s just you all take care of your patients and learn how to manage it?

SHULMAN: Managing the toxicities is straightforward with immunotherapy. I think with the TKIs, I’ve always had a low threshold [to] just stop and hold, let it resolve, and then restart at a lower dose. However, I think sometimes if you get behind and if they develop bad hand-foot syndrome it seems to never go away.

REFERENCES
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

**ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE**

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial

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**IMPORTANT SAFETY INFORMATION**

**DARZALEX® AND DARZALEX FASPRO®: CONTRAINDICATIONS**

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

**DARZALEX®: Infusion-Related Reactions**

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute...
**Powerful efficacy to start the treatment journey**

After a median ~30 months* of follow-up, mPFS was not reached with DARZALEX® + Rd vs 31.9 months with Rd alone.†

- 70.6% of patients had not progressed with Rd vs 55.8% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)§

44% reduction in the risk of disease progression or death with Rd vs Rd alone (HR=0.56; 95% CI, 0.43–0.73; P<0.0001)

**Demonstrated safety profile**

(median treatment duration of 25.3 months)†

- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia

- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

**MAIA Study Design:** A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.¶

- Kaplan-Meier estimate.

**Efficacy results in long-term follow-up**

At median ~5 years (56 months)‡ of follow-up, mPFS was not reached with DRd vs 34.4 months with Rd alone.‡

- 53% of patients had not progressed after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35)¶

47% reduction in the risk of disease progression or death with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

**Safety results in long-term follow-up**

(median treatment duration of 47.5 months)‡

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

**With an ~3 to 5 minute subcutaneous injection.**

DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.

**See the latest data rolling out. Visit FrontlineMomentum.com**

appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

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

**DARZALEX FASPRO®: Hypersensitivity and Other Administration Reactions**

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

**Systemic Reactions**

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%; Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO® administration. Delays in systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-Threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®. Consider administering

*CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRR= infusion-related reaction; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

**With an ~3 to 5 minute subcutaneous injection.**

DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.

**See the latest data rolling out. Visit FrontlineMomentum.com**
corticosteroids and other medications after the administration of DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed [defined as occurring the day after administration] systemic and immunoabsorption-related reactions.

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

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia
DARZALEX® and DARZALEX FASPRO® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX FASPRO®: Interference With Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX® and DARZALEX FASPRO®.

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

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

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

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

DARZALEX FASPRO®: ADVERSE REACTIONS
In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dysgeusia, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX FASPRO® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS
DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

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

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.
DARZALEX® (daratumumab) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
DARZALEX is indicated for the treatment of adult patients with multiple myeloma:
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS
DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation [see Warnings and Precautions].

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported [see Adverse Reactions].

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision [see Adverse Reactions].

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was the same as used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4<1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reaction at Week 1 was 12%, with 38% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 2.4 hours for the subsequent infusions.

Pre-mEDIATE patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion [see Dosage and Administration (2.3) in Full Prescribing Information]. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion [see Dosage and Administration (2.4) in Full Prescribing Information].

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions [see Dosage and Administration (2.3) in Full Prescribing Information]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease [see Dosage and Administration (2.3) in Full Prescribing Information].

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

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

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX [see Dosage and Administration (2.1) in Full Prescribing Information].

Neutropenia
DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia
DARZALEX may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Infusion-related reactions [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

Clinical Trials Experience

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥25%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.4 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd). Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).
Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (% of N=283)</th>
<th>Rd (% of N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>57 (0)</td>
<td>46 (0)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>41 (1)</td>
<td>36 (1)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>32 (1)</td>
<td>23 (0)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Infections</td>
<td>Upper respiratory tract infection</td>
<td>52 (2)</td>
<td>36 (2)</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>29 (3)</td>
<td>21 (1)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>26 (14)</td>
<td>14 (7)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>18 (2)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Infusion-related reactions</td>
<td>41 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>41 (2)</td>
<td>33 (1)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>40 (8)</td>
<td>28 (4)</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>32 (4)</td>
<td>25 (3)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>23 (2)</td>
<td>18 (2)</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>13 (0)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>34 (3)</td>
<td>26 (3)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>29 (1)</td>
<td>22 (1)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>32 (3)</td>
<td>20 (1)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>30 (&lt;1)</td>
<td>18 (0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Periphera sensory neuropathy</td>
<td>24 (1)</td>
<td>15 (0)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>19 (1)</td>
<td>11 (0)</td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>16 (0)</td>
<td>8 (0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>22 (1)</td>
<td>15 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>14 (6)</td>
<td>8 (3)</td>
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<tr>
<td></td>
<td>Hypocalcemia</td>
<td>14 (1)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>13 (6)</td>
<td>7 (4)</td>
</tr>
</tbody>
</table>

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (% of N=283)</th>
<th>Rd (% of N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>52 (13)</td>
<td>57 (24)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>92 (36)</td>
<td>87 (32)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95 (42)</td>
<td>87 (32)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>67 (22)</td>
<td>67 (22)</td>
</tr>
</tbody>
</table>

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

Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (% of N=283)</th>
<th>Rd (% of N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>43 (5)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (1)</td>
<td>14 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>21 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td>26 (1)</td>
</tr>
</tbody>
</table>

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

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.
Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th></th>
<th>DRd (N=238)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95</td>
<td>42</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>92</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>13</td>
</tr>
</tbody>
</table>

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

Hepatitis A Virus (HAV) Reactivation

Hepatitis A virus reactivation was reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials. The incidence of hepatitis A was not different between treatment arms. No cases of acute liver failure have been observed.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation was reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials. Postmarketing surveillance for HBV reactivation is continuing.

Hepatitis C Virus (HCV) Reactivation

Hepatitis C virus reactivation was reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials. In postmarketing use, the incidence of hepatitis C was not different between treatment arms. No cases of acute liver failure have been observed.

Postmarketing Experience

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

Immune System disorders: Anaphylactic reaction, IRR (including deaths) Gastrointestinal disorders: Pancreatitis Infections: Cytomegalovirus, Listeriosis

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with diethytohlolate (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying all antibodies using DTT-treated RBCs.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial ascertainment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematologic evaluation is completed.

Data

Animal Data

Monoclonal antibodies were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetal-maternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations).

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.
Contraception
Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

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

Geriatric Use
Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients [see Adverse Reactions]. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

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

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

Neutropenia
Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia
Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding [see Warnings and Precautions].

Interference with Laboratory Tests
Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation
Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again [see Adverse Reactions].

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

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864
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DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are not eligible for autologous stem cell transplantation and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

In a pooled safety population of 888 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2-3.2%, Grade 3: 1%). Severe systemic administration-related reactions occurred in 6% of patients with the first injection, 3% with the second injection and dexamethasone, and 1% with subsequent injections. The median time to onset was 1 hour (range: 0 minutes to 3 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypotension, dyspnea, tachycardia, and tachycardia, and ocular adverse reactions, including conjunctivitis, blurred vision, and ocular pain. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chill, vomiting, nausea, hypotension, and blurred vision.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If severe or life-threatening reactions occur, interrupt DARZALEX FASPRO and refer the patient to an ophthalmologist for immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO. Monitor local reactions in patients with histamine-1 receptor antagonist, acetylsalicylic acid, corticosteroids (see Dosage and Administration (2.5) in Full Prescribing Information) and monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening reaction (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.5) in Full Prescribing Information).

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum (see References [11]). The determination of a patient's ABO and Rh blood type are not impacted (see Drug Interactions).

Note: Blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO (see Dosage and Administration (2.1) in Full Prescribing Information).

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

- Hypersensitivity and Other Administration Reactions (see Warnings and Precautions).
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis (see Warnings and Precautions).
- Neutropenia (see Warnings and Precautions).
- Thrombocytopenia (see Warnings and Precautions).

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

Dosage interruptions due to an adverse reaction occurred in 83% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increase. The most common adverse reactions (≥20%) were fatigue, diarrhea, and upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.
Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>52</td>
<td>5a</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2a</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3a</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5a</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2a</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionb</td>
<td>43</td>
<td>3a</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitisd</td>
<td>14</td>
<td>2a</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3</td>
<td>2a</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Coughb</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
<td>2a</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
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<tr>
<td>Insomnia</td>
<td>17</td>
<td>5a</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9a</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

a Fatigue includes asthenia, and fatigue.
b Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
c Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
d Bronchitis includes bronchitis, and bronchitis viral.
e Dyspnnea includes dyspnea, and dyspnea exertional.
f Cough includes cough, and productive cough.
g Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:
- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain
- Nervous system disorders: dizziness, headache, paresthesia
- Skin and subcutaneous tissue disorders: rash, pruritus
- Gastrointestinal disorders: abdominal pain
- Infections: influenza, sepsis, herpes zoster
- Metabolism and nutrition disorders: decreased appetite
- Cardiac disorders: atrial fibrillation
- General disorders and administration site conditions: chills, infusion reaction, injection site reaction
- Vascular disorders: hypotension, hypertension

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
<td>5a</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

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

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously during organogenesis, which is 45 times higher than the human dose.

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

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

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, nausea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program [see Use in Specific Populations].

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

Product of Switzerland

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Horsham, PA 19044

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