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Gasparetto Discusses Sequencing Selinexor in Relapsed/Refractory Multiple Myeloma

**CASE**

- In 2019, a 70-year-old White woman was given a diagnosis of stage I multiple myeloma.
- Fluorescence in situ hybridization showed deletion 17p (del[17p]).
- The patient declined autologous stem cell transplant and received lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone.
- Her best response was a very good partial response (VGPR).
- Lenalidomide maintenance continued.

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<tr>
<th>Test</th>
<th>Value (reference)</th>
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<tr>
<td>Bone marrow abnormal plasma cells</td>
<td>30%</td>
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**Laboratory results**

- Calcium 10 mg/dL (9-10.5)
- Serum creatinine 1.3 mg/dL (0.6-1.3)
- Creatinine clearance 39 mL/min
- Hemoglobin 6 g/dL (13.5-17.5)
- IgA lambda FLC 200 mg/dL (0.57-2.63)
- M protein 3 g/dL (IgAL)
- Albumin 3.4 g/dL (3.3-5.7)

**Imaging**

- Skeletal survey L4-L5 compression fractures

**Second relapse:**

- Patient received daratumumab (Darzalex) plus pomalidomide (Pomalyst) with a best response of VGPR.
- One year later (2022) second relapse was discovered.
- Kidney function continues to decline.

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</table>

**Laboratory results**

- Calcium 10 mg/dL (9-10.5)
- Serum creatinine 2.3 mg/dL (0.6-1.3)
- Hemoglobin 8 g/dL (13.5-17.5)
- Creatinine clearance 20 mL/min (97-137)
- IgA lambda FLC 260 mg/dL (0.57-2.63)
- M protein 1.5 g/dL (IgAL)
- Albumin 3.3 g/dL (3.3-5.7)

**Imaging**

- Skeletal survey No additional lesions
- FDG PET-CT New spinal osteolytic lesions

**Two years later:**

- Patient continuing on lenalidomide maintenance.
- On routine follow-up, the patient reported having mild fatigue but continued to work full time.
- Bone marrow plasma cells, light chains, and M protein rising.
- Kidney function worsening (now stage IV chronic kidney disease).
The number of patients with high-risk cytogenetics was quite high, about 50% of the population, because patients with a 1q21 amplification were included, [as were patients with] del(17p), t(14;16), and t(4;14). The median age was similar between the experimental and control arms at 66 years vs 67 years, respectively. The ECOG performance status was good, between 0 and 1 for most of the patients; about 10% of the patients in each arm had an ECOG performance status of 2.

There was an equal distribution of disease stage at screening between the experimental and control arms [for stage I or II, 89% vs 86%, respectively; for stage III, 6% vs 8%, respectively]. In both arms, the time since diagnosis was [almost] 4 years in both arms. Also in both arms, the percentage of patients who had received 1 prior line of therapy was about 50% and the percentage who had received 2 prior lines was [about 30%].

In the experimental and control arms, the percentage who had received 3 prior lines was 16% and [21%], respectively. Most of the patients [in both arms] had been exposed to a PI, bortezomib, carfilzomib [Kyprolis], or ixazomib [Ninlaro]. Only about 6% of the patients in the experimental arm, vs 3% in the control arm, were refractory to daratumumab. [Other possible prior therapies were] the immunomodulatory imide drugs [IMiDs] lenalidomide and pomalidomide [Pomalyst].

What did the data reveal about the efficacy of this regimen in the overall population and in various subgroups?

The primary end point of the study, PFS, was met. The median PFS for the experimental arm was [13.93 months; 95% CI, 11.73-not evaluable] vs [9.46 months; 95% CI, 8.1-10.78] for the control arm [HR, 0.70; 95% CI, 0.53-0.93; P=.0075].

In this study, the selinexor combination benefited patients across subgroups. Subgroup analyses are important to me when I review data because I’m [considering whether the experimental] therapy is appropriate for my particular patients, given their age, performance status, and other factors. An important [factor in the patient population of this study is] prior exposure. Remember, the percentage of patients who had received daratumumab was small, but these are difficult patients to treat. Before the introduction of these new drugs, the projected OS of daratumumab-refractory patients was less than 8 months.

Now, with the addition of this new therapy, we can [extend] the life of daratumumab-refractory patients. [In the BOSTON study, such patients demonstrated a HR of 0.49 [95% CI, 0.13-1.84]. Among the subgroups defined by cytogenetic abnormalities, patients with del(17p) also performed well [HR, 0.38; 95% CI, 0.16-0.86]. Patients with t(4;14) also experienced a benefit, though it was a little less [HR, 0.66; 95% CI, 0.31-1.43]. Additionally, there was a benefit for patients with the 1q21 amplification, which is becoming an important genetic [biomarker], and also a benefit for patients with moderate renal insufficiency, ie, an estimated glomerular filtration rate between 30 and 60 mL/min.«
Finally, benefit was observed among all subgroups defined by the number of prior lines of therapy and by the presence or absence of prior stem cell transplant. The ORR in the experimental arm, featuring selinexor, dexamethasone, and once-weekly bortezomib, was [76.4%]. In contrast, the ORR in the control arm, featuring only dexamethasone plus bortezomib, which was initially given twice weekly, was [62.3%].

The depth of response was a little better in the experimental arm than in the control arm, with 44.6% vs 32.4% of patients, respectively, demonstrating a very good partial response [VGPR] or better. Patients in the experimental arm also responded faster than those in the control arm, with a median time to response of 1.1 months vs 1.4 months, respectively. The median DOR was 20.3 months vs 12.9 months, respectively, [demonstrating a] definite impact [of the experimental regimen] on the DOR.²³

A prespecified analysis was performed to compare the outcomes of standard-risk patients with those of patients with high-risk cytogenetic abnormalities. For the high-risk patients, median OS was [22.87] months in the experimental arm vs [24.84] months in the control arm [HR, 0.87; 95% CI, 0.52-1.46; P=.304]; median OS was not reached [NR] for either arm in the standard-risk cohort [HR, 0.75; 95% CI, 0.46-1.23; P=.129].

The ORRs were similar between the high-risk and standard-risk cohorts [for a given regimen], as were the percentage of patients achieving VGPR or better and the percentage of patients achieving CR. The median DOR [with the experimental regimen] was 13 months for the high-risk group and NR for the standard-risk group, and the time to next therapy was [14 months vs 18 months, respectively].⁴ These are well-respected data, and I think the outcome was impressive, even in patients with del(17p).

Another important analysis was performed to investigate the outcomes for] patients with renal impairment. Among patients treated with the experimental regimen, median PFS was [16.62] months for patients with moderate renal insufficiency and [13.24] months for patients with normal renal function.

[Additionally,) the ORRs and depths of response were similar [between these groups], so the combination was tolerated. Now, in patients with severe renal impairment, the [rates of PFS, OR, and VGPR] were lower, of course, but the median DOR was 20.27 months vs 15.34 months for patients with normal renal function and NR for patients with moderate renal insufficiency.⁵

What did the BOSTON trial reveal about the toxicity profile of selinexor?

In the BOSTON study, in which selinexor was administered once a week, the adverse events [AEs] were like those in the initial STORM study [NCT02336815], wherein selinexor was [administered twice a week in combination with] dexamethasone.

[The AEs in the BOSTON study were] mitigated by the fact that the selinexor was given only once a week. In fact, all the nonhematologic AEs, [most notably] nausea and fatigue, which are common with this drug and affected most of the patients in this trial, were limited to grades 1 and 2 for most patients [in the experimental arm]. Fatigue and nausea of grade 3 or 4 affected only 13% and 8% of these patients, respectively. [Of course], myelosuppression [is to be expected], and [indeed], thrombocytopenia was observed in 60% of the patients in the experimental arm, with [39%] developing thrombocytopenia of grade 3 or 4.

This was higher than what was observed in the control group [27% for all grades, 17% for grade 3 or 4]. Additionally, anemia was a bit more pronounced with the addition of selinexor; [anemia of all grades affected 36% of the experimental group and 23% of the control group].

The most common AEs of grades 3 or 4 were thrombocytopenia, anemia, neutropenia, pneumonia, [and] fatigue. Discontinuation due to AEs affected 21% of the patients in the selinexor arm and 16% in the control arm. The most common reasons for discontinuation were peripheral neuropathy, fatigue, nausea, vomiting, decreased appetite, and thrombocytopenia. Finally, dose modification was common in this trial, with 89% of the patients on the selinexor arm receiving dose modification and [most showing subsequent] improvement of the AEs.²

How do you counsel patients who will receive selinexor?

With selinexor, I always think about gastrointestinal toxicity, particularly nausea, which can be profound at the beginning [and which can lead to] decreased appetite, weight loss, and hyponatremia, and [I also think about] myelosuppression.⁶

In the STORM study, which employed a twice-weekly administration, the patients needed 3 antiemetics [as soon as they began treatment] with the experimental regimen. When selinexor was given once a week, the toxicity was mitigated. When we use this reduced regimen, we use 2 antiemetics for about the first month or 2, ondansetron [Zofran] in combination with olanzapine [Lybalvi] at bedtime, but after about the first month, when the patient is tolerating therapy, we make the proper dose adjustment. Then the patient doesn’t need the second antiemetic anymore.

Still, you do need to counsel your patient by discussing the new drug and what to expect. We counsel patients about nutrition and intravenous [IV] fluid support and we monitor their blood count. Because of the myelosuppression, particularly the thrombocytopenia, it is important to monitor the blood count. It is also important to monitor the sodium level. We still see some hyponatremia even with the once-weekly dosing...
schedule, so monitor electrolytes. Also, monitor the patient’s nutritional status and counsel the patient about caloric intake and hydration. We use a fair amount of IV fluids, particularly in the first month. I always tell patients that at least some of the symptoms are going to be worse for the first month or 2, but when we modify the dose as necessary, they will find that they become adjusted.

How does the dosing schedule of selinexor affect its toxicity profile and efficacy?

[The dosing of selinexor greatly affects the profile of grade 3 or 4 AEs.] In the STORM study, wherein 80 mg of selinexor was given twice a week to heavily pretreated patients, thrombocytopenia of grade 3 or 4 affected [58%] of the patients. In the BOSTON study, wherein 100 mg of selinexor was given once a week, only 39% [of the patients were thus affected]. [High-grade neutropenia] affected 21% and 9% of the patients in the respective studies, and the patients in the BOSTON study also experienced less [high-grade] fatigue and hyponatremia. Importantly, most patients required dose reductions from 100 mg to 80 mg or 60 mg [Table 2-7].

I think you will see, when you start to treat more patients with this combination, that you reach a dosage that becomes the most used dose, and in my clinic that dose is about 60 mg. Some interesting data show that the patients who required selinexor dose reduction had a longer PFS than did the patients who were maintained on 100 mg without dose reduction [16.6 months vs 9.2 months, respectively (HR, 0.5678; 95% CI, 0.3614-0.8919; P = .0065)]. Also, the ORR was better for patients with dose reduction than for patients without dose reduction [81.7% vs 66.7%, respectively].

The message here was simply that the patients were able to tolerate selinexor at the lower dose, adjust to that dosage, and stay on therapy longer. That translates to a better, deeper response and longer PFS. So the recommended starting dose is 100 mg. I tell my patients that is a loading dose for the first month and [that we will make] adjustments based on their AEs and [thus be] able to sustain therapy for several months [or possibly even for] a few years.

What data support the use of selinexor in combination with drugs other than bortezomib and dexamethasone?

We can use selinexor in different combinations on the basis of the data from the STOMP trial [NCT01558427]. This was a phase 1b/2 trial in which selinexor was used in combination with different backbone treatments for myeloma (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab). Patients were assigned to a particular combination based on their prior lines of therapy. It became clear from the beginning that once-weekly administration of selinexor was sufficient.

The dosage was a little lower [when selinexor was used] with the IMiDs because there is more myelosuppression; the selinexor dose was 60 mg when it was used in combination with lenalidomide, 60 or 80 mg in combination with pomalidomide, 80 [or 100 mg] with carfilzomib, and [100 mg] with bortezomib and with daratumumab.

This was important because we were able, in the phase 1 portion of the study, to establish the recommended dose for phase 2, and then [we could] expand the study, enrolling more patients. The combination of selinexor plus carfilzomib and dexamethasone produced an ORR of 78%, and about one-third of the patients achieved a VGPR. Many patients who received this combination had previously received an anti-CD38 antibody and some were refractory, yet the ORR in this subpopulation was 65% and the PFS was 15 months.

| TABLE. Significance of Selinexor Dosing to Grade 3-4 Toxicities |
|------------------|------------------|
|                  | STORM (Sd)       | BOSTON (SVd)    |
|                  | 160 mg (80 mg biweekly) | 100 mg once weekly |
| Dosing           | 100 mg once weekly | 100 mg once weekly |
| Median number of prior lines of therapy, n | 7 | 2 |
| Grade 3-4 AEs    |                  |                  |
| Thrombocytopenia | 58%              | 39%              |
| Neutropenia      | 21%              | 9%               |
| Nausea           | 10%              | 8%               |
| Fatigue          | 25%              | 13%              |
| Hyponatremia     | 22%              | 14%              |

AEs, adverse events; Sd, selinexor and dexamethasone; SVd, selinexor, bortezomib, and dexamethasone.
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Roundtable Discussion: Iams Considers Platinum Rechallenge or Other Therapy for Relapsed ES-SCLC

**CASE SUMMARY**

A 58-year-old, moderately active man presented with worsening shortness of breath, persistent dry cough, and fatigue. He was a smoker with a 30 pack-year history. At this point, he was assessed to have an ECOG performance score of 1.

Chest x-ray showed opacity in left lung, whereas a chest CT showed a hilar mass, with invasion of the left pulmonary artery and 3 contralateral lung metastases. A brain MRI was negative. A bronchoscopy with transbronchial biopsy of the hilar mass and a contralateral metastasis confirmed a diagnosis of extensive-stage small cell lung cancer (ES-SCLC). He received 4 cycles of carboplatin plus etoposide plus atezolizumab (Tecentriq) and initially achieved a partial response.

**IAMS:** It is a pretty even split among participants over prophylactic cranial irradiation. I will cite a couple components. I do usually have the patients have a conversation with a radiation oncologist. One unique thing about this case that jumped out at me was that it did not seem like the patient had high disease burden overall, with predominantly intrathoracic disease.

Potentially, there’s a case there, to increasing the time to brain metastasis. But there are phase 3 randomized data of a lack of survival benefit in ES-SCLC with [prophylactic cranial irradiation](#)

that are being reevaluated in the SWOG S1827 study [NCT04155034]. We will have additional data commenting on those results [soon].

**ROSENFELD:** I typically scan every 2 months. It is such an aggressive disease that I do 2 months instead of 3 months.

**FLEISCHMAN:** [Could this depend on] what you see in his partial remission PET scan?
**IAMS:** Potentially, depending on the depth of response, that could help guide frequency. Guidelines are currently allowing that 2-month interval for ES-SCLC.²

**NAKHOUL:** I scan every 2 months.

**FLEISCHMAN:** I think it’s fine, but we do not know [whether] more frequent scanning is going to change overall survival [OS].

**IAMS:** We will touch on that bit tangentially, with timing of relapse and decisions on therapy.

**CASE UPDATE**

Seven months after the last cycle of platinum chemotherapy, shortness of breath returned with right upper quadrant pain and midback pain. A CT scan of the chest, abdomen, and pelvis showed hematogenous metastases in the liver and adrenal glands. He was still negative for brain metastases. Laboratory results were within normal limits. His ECOG performance score was still 1.

**DISCUSSION QUESTION**

How do we define platinum-sensitive vs platinum-resistant disease?

**KHASHAWNEH:** I would consider them platinum sensitive if they progressed more than 6 months from their last platinum therapy.

**IAMS:** Absolutely. The NCCN guidelines have the 6-month interval noted. One of the tensions in the data and the guidelines is a lot of the data come out attempting to define it as a 3-month interval, so it can be a struggle to interpret the guideline of 6 months, [whereas] the data we have is at 3 months.

**DISCUSSION QUESTIONS**

- What are your general expectations going into a platinum rechallenge?
- What factors would influence you to use or not use each therapeutic option as second-line therapy?
  - Platinum-free interval
  - Tolerance to prior therapy
  - Performance score/frailty
  - Comorbidities

**GALLAGHER:** Unfortunately, the PFS may be half as long [for platinum rechallenge].

**IAMS:** Yes.

**MAHESHWARI:** Can we combine the platinum with irinotecan [Camptosar] in these situations?

**IAMS:** For the platinum rechallenge, I think that would be reasonable. The platinum backbone would be the main intended component, so I think so.

**IAMS:** When you are thinking about platinum rechallenge, do you feel like a longer time since the last platinum makes a stronger case to do the rechallenge? Or if they are right at the 6-month interval, for example, would you be more likely to choose a different agent?

**MAHESHWARI:** I think the longer the disease-free interval, the more likely the patient is going to respond to the cisplatin backbone treatment, along with the irinotecan. I prefer...
irinotecan in situations where the patient already got [etoposide]. I give it day 1 and day 8, every 21 days.

IAMS: I do not have specific data to comment on that question. What would be the significance of a complication that would preclude platinum rechallenge, in your opinion?

MAHESHWARI: If we have used a cisplatin-based treatment initially and they have significant hearing issues, neuropathy, or even renal insufficiency, that will impact the decision. On the other hand, if you give carboplatin-based treatment and the patient has significant thrombocytopenia or blood issues, that can definitely change.

IAMS: The question of performance status and frailty [relates to] the tolerance of lurbinectedin vs a platinum rechallenge. For a patient with a performance status of 2, which many of these patients are at relapse, do you have more comfort with a certain regimen?

FLEISCHMAN: One of the things I sometimes go on is whether they have to travel and whether they would rather have an oral regimen or [intravenous]. I mean at this point, you are buying months of survival. You do not want to make a patient terribly ill or take away their quality of life [QOL] to do that.

IAMS: Yes. As they proceed in the course of SCLC, what you are gaining in QOL is declining, so the attention to QOL is escalating, for sure.

MAHESHWARI: With a performance score of 1 or 2, you still can rechallenge it based on the toleration. On the other hand, if a patient is [declining], I still prefer combination drugs if they have more than 6-month times [of response]. The reason why is because it is SCLC. I have not seen a great response from topotecan, so there is another reason. When we reach [for] the topotecan, pancytopenias can be challenging.

FLEISCHMAN: [This is true of] lurbinectedin, as well.

IAMS: Yes, we will continue to discuss individual thoughts on lurbinectedin. The febrile neutropenia was not too bad for the [overall] rates of neutropenia, but the rate of neutropenia alone was quite prominent [From the Data^4].

FLEISCHMAN: It depends on your patient population. Once they get severe enough neutropenia, they say there were not that many febrile ones. But I wait until I have my patients, [and I expect] they are all going to be febrile.

FLEISCHMAN: Why couldn’t they improve PFS, though? It looks exactly the same.

IAMS: I think that comes back to there being a subgroup of patients who have any degree of treatment sensitivity. I could launch into a bit of a tangent about the SCLC subtypes. A lot of [National Cancer Institute]–funded research is going into delineating the 4 subtypes of SCLC. These are defined by unique transcription factor profiles. What I can offer is: the cohort that is benefiting in OS—maybe they are a particular predominant subtype that is a minority subtype. So, the median PFS is still bad, but there is some subgroup of individuals, or within an individual, where there is an intratumoral subtype that is manageable.

FLEISCHMAN: But we have to go back and reanalyze all the patients for transcriptome analysis.

IAMS: The best guess is the short answer, and that being impossible is the implication. Tumors are so hard to come

**FROM THE DATA**

During the phase 2 basket trial (NCT02454972) of lurbinectedin, neutropenia occurred in 75 of 105 patients with SCLC (72%), including 27 (26%) with grade 1 or 2 neutropenia, 22 (21%) with grade 3 neutropenia, and 26 (25%) with grade 4 neutropenia. Treatment-related febrile neutropenia was reported in only 5 patients, 2 (2%) of whom had grade 3, and 3 (3%) of whom had grade 4 febrile neutropenia.
by to do in-depth analyses like that, so we are going to need more blood-based monitoring in SCLC.

**FLEISCHMAN**: Can you do that based on the blood-based circulating tumor DNA [ctDNA]? Don’t you need real tissue?

**IAMS**: That is one of the main areas on the horizon. I think this comes back to clinical meaning, hopefully within the next 5 to 10 years. With methylation profiling, there is some interesting validation work going on right now.

Nothing has been published yet, but I know there are [studies] aimed at high-impact publications to RAI2 [retinoic acid-induced 2]-link subtype by ctDNA methylation profiling, which could provide some delineation of what transcription factor programs are activated. Anyway, there is more to come on that. That would be a bit of a Rosetta Stone of the issue.

**DISCUSSION QUESTIONS**

- If you have used lurbinectedin, please discuss your experience.
- What types of patients have you used lurbinectedin for?
- How do you consider lurbinectedin for patients who are platinum sensitive?

**KHASAWNEH**: I’ve used it in a couple patients. Two of the 4 or 5 patients had stable disease, and the data seemed to be comparable with my personal experience. From a tolerance standpoint, I find myelosuppression and fatigue are the most common adverse events [AEs], but I did not see any significant AEs causing discontinuation of the drug.

**IAMS**: I have had a similar experience, where it is fatigue predominantly, and certainly cytopenias. We had debated whether to administer G-CSF [granulocyte colony-stimulating factor] as primary prophylaxis in the use of the treatment, but we had had opted to some degree of primary prophylaxis, so it is not necessarily primary prophylaxis for lurbinectedin.

**FLEISCHMAN**: Although the percentages are high enough that, based on the old criteria for G-CSF, you could justify it because it is already greater than 40%.

**IAMS**: The grade 3 or higher rate of neutropenia is [46%].

**FLEISCHMAN**: In lymphoma, we would say that is high enough that you can get primary prophylaxis.

**IAMS**: The hypothesis of selection bias of trials is probably the primary driver of why their febrile neutropenia rate was so low, despite the severe neutropenia.

**FLEISCHMAN**: They are all study patients. They are always going to be better than patients I am going to get, a lot of whom would probably not even get into a clinical trial.

**IAMS**: Exactly. Any additional comments on the use of lurbinectedin or just relapsed SCLC, in general?

**MAHESHWARI**: I would probably use it in the third-line setting.

**FLEISCHMAN**: I think so, yes.

**IAMS**: That would align with the guidelines we reviewed.

**TIAN**: Are you going to comment on the trilaciclib [Cosela] for use in the frontline setting?

**IAMS**: As a new alternative to G-CSF for myelopreservation… it is an interesting point. I have not used it, but I am curious [whether] others use it. There was a FDA approval of trilaciclib. It induces cellularsenescence to preserve from cytopenias, particularly during SCLC regimens. Has anyone used trilaciclib?

**TIAN**: I have used it once. The patient ended up getting transfusion support, so I just wanted to find out what other physicians are doing.

**IAMS**: Some of the data showed not only decreased severity of neutropenia but also decreased red blood cell–transfusion requirements with trilaciclib. There are some interesting data. We ultimately did not add it to our formulary [at Vanderbilt University Medical Center].

**DISCUSSION QUESTIONS**

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

**IAMS**: We are discussing the platinum-sensitive setting, so it is going all the way back to 7 months since last platinum-based therapy. What if this patient had brain metastases? Would your selection of platinum rechallenge, lurbinectedin, topotecan, or CAV [cyclophosphamide, doxorubicin, and vincristine] differ based on brain metastasis?
ROSENFELD: Are there data on lurbinectedin cross-comparison trials? Do you feel like one agent is better with brain metastases, whether it is topotecan or CAV?

IAMS: No.

FLEISCHMAN: Temozolamide [Temodar] has CNS [central nervous system] penetration. Of course, it is oral, so that is also sometimes convenient. But are you talking about uncontrolled brain metastases or ones that have been pretty well treated with Gamma Knife [stereotactic radiosurgery], or [otherwise] controlled? It makes a difference.

IAMS: Let us say uncontrolled, with any hope for CNS efficacy. But I do agree with temozolomide, for sure. There are some interesting data—not relevant to relapse, because most of them have received ICIs, as well—but there is a subgroup of patients whose data sets are being put together, more so in non–small cell lung cancer, of ICI efficacy for patients with CNS metastases. But I have not seen that as much in SCLC.

DISCUSSION QUESTIONS

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

IAMS: What do you view as the most critical unmet need?

ROSENFELD: Everything.

IAMS: [We need to] help them live longer and better.

MAHESHWARI: Yes, we have not had [many] breakthroughs, as long as we have been treating SCLC.

FLEISCHMAN: [We also need] better prediction. The 25% or 20% that are going to do well with immunotherapy are going to be [longer-term survivors]. But we do not have to treat everybody; we already know ahead of time they are not going to do well. I think that would be good. I do not know [whether] the patients would appreciate it, but it would be helpful.

MAHESHWARI: I had a patient who had a significant skin rash, [and] I had to stop the treatment. He had ES-SCLC. He is almost 1.5 years out. He is doing remarkably well. I still believe patients who get a lot of AEs may have a better response.

IAMS: Yes. There are intriguing and well-replicated data sets along those lines, regarding immune-related AEs, except in the setting of pneumonitis with lung cancer, which is typically very bad prognostically and very difficult to manage. Besides that, there are some compelling data sets displaying improved antitumor efficacy for basically any other immune-related AE.

To cite the major studies going on in the field, novel ICIs outside of PD-1 and CTLA-4 are being added. Anti-TIGIT [T-cell immunoglobulin and ITIM domain] antibodies is a big first-line trial [SKYSCRAPER-02; NCT04256421]. I am not sure we are going to be able to gain much more from the PD-1/platinum-etoposide backbone, but we will see.

Adding PARP inhibitors to that ICI maintenance is being assessed [in a study; NCT04790955]. Another interesting [ongoing] study is lurbinectedin being added to checkpoint inhibitor maintenance [IMforte; NCT05091567]. Is there a cohort of patients within that maintenance group who could achieve further benefit by adding lurbinectedin to the checkpoint inhibitor?

Those are the big trials I am aware of in ES-SCLC, at least in the first-line setting. Then we have a lot of phase 1 trials, with no clear leader of the pack, for the relapsed setting. Some interesting work is being done for antibody-drug conjugates, bispecific T-cell engagers, and immune effector cells, like [chimeric antigen receptor] T-cell therapies. Those are all being evaluated but nothing has demonstrated breakthrough data, that I have seen so far.

FLEISCHMAN: The antigen is unique to those cells. I would be surprised if you could find one.

IAMS: There is an interesting case for DLL3 [delta-like ligand 3]. The main cross-reactivity of DLL3 is neural, which is problematic. But interestingly, the main toxicities that were seen when an anti-DLL3 antibody-drug conjugate was assessed were severe pericardial and pleural effusions.8 The reasons are unclear as to why that happened, but there is a lot of investment in trying to use bispecific T-cell engagers for DLL3. That is the lead antigen I am aware of, but there has not been a breakthrough yet.

The other complicating factor when we think about the paradigm of SCLC subtypes is that DLL3 does not consistently track with subtypes, so it is going to be hard to link attempts at going after that specific antigen with subtypes. But there are interesting data that 1 subtype could be particularly immunogenic, and it is a little too good to be true. It looks like it is [approximately] 15% of the patients, a similar cohort you would hypothesize has that clear benefit with immune therapy. We will see how that could play out clinically, if that can be replicated.
In adult and pediatric patients 12 years and older

**Intervene With Jakafi at the First Sign of Initial Systemic Treatment Failure for cGVHD**

*Timely Diagnosis and Early Intervention Are Critical to Prevent Potentially Irreversible Organ Damage*

Jakafi® (ruxolitinib) 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.

**REACH3 Primary Endpoint: ORR at Week 24**

<table>
<thead>
<tr>
<th>ORR through Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% (116/165) with Jakafi vs 57% (94/164) with BAT</td>
</tr>
</tbody>
</table>

*In the Jakafi Prescribing Information, efficacy was based on ORR through week 24 (Cycle 7 Day 1)*

**REACH3 Subgroup Analysis: ORR by Baseline Disease Severity at Week 24**

<table>
<thead>
<tr>
<th>Baseline Disease Severity</th>
<th>Jakafi</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate GVHD</td>
<td>49.4%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Severe GVHD</td>
<td>16.7%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

*ORR=overall response rate; PR=partial response.

**IMPORTANT SAFETY INFORMATION**

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi.
- Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.
- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial...
Overall Response Rates Were Higher With Jakafi at Week 24 Regardless of Organs Involved at Baseline vs BAT\(^3\)

REACH3 Subgroup Analysis: ORR at Week 24 by Baseline Organ Involvement\(^3\)\(^2\)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Jaka/f_i</th>
<th>BAT</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>52.9</td>
<td>51.5</td>
<td>1.01-11.43</td>
<td>1.30, 4.54</td>
</tr>
<tr>
<td>Mouth</td>
<td>25.7</td>
<td>29.1</td>
<td>0.68-18.10</td>
<td>0.68, 18.10</td>
</tr>
<tr>
<td>Eyes</td>
<td>45.4</td>
<td>40.5</td>
<td>1.51-11.43</td>
<td>1.19, 8.51</td>
</tr>
<tr>
<td>Lungs</td>
<td>26.1</td>
<td>25.4</td>
<td>0.68, 18.10</td>
<td>1.19, 8.51</td>
</tr>
<tr>
<td>Joints and Fascia</td>
<td>43.8</td>
<td>16.7</td>
<td>2.43-6.77</td>
<td>1.30, 4.54</td>
</tr>
<tr>
<td>Liver</td>
<td>47.6</td>
<td>27.5</td>
<td>3.24-11.43</td>
<td>1.86, 5.67</td>
</tr>
<tr>
<td>GI Tract</td>
<td>51.3</td>
<td>25.0</td>
<td>3.52-11.43</td>
<td>1.86, 5.67</td>
</tr>
<tr>
<td>Genital Tract</td>
<td>42.9</td>
<td>17.6</td>
<td>2.71-6.77</td>
<td>1.86, 5.67</td>
</tr>
</tbody>
</table>

*Patients with >1 affected organ were counted in each organ subgroup. ORR was calculated as the number of patients with a partial or complete response divided by the total number of patients in each subgroup.*

References:


In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections.

- 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.

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

References:


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

INDICATIONS AND USAGE Myeloﬁbrosis: Jakafi is indicated for treatment of intermediate- or high-risk myeloﬁbrosis (MF), including primary MF, post-polycythemia vera (PV) and post-essential thrombocythemia (ET) in adults. Polycythemia Vera: Jakafi is indicated for treatment of polycythemia vera (PV) in patients who have had an inadequate response to or are intolerant of hydroxyurea.

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.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS: Thrombocytopenia, Anemia and Neutropenia: Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. See Adverse Reactions (6.1) in Full Prescribing Information. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary. See Dosage and Administration (2) in Full Prescribing Information. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10^9/L) is 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.

Discontinuation of Treatment with Jakafi: 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.

Myeloﬁbrosis: The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 391 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 69% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia (see Table 2).

Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent 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 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>All Grades (%)</th>
<th>Grade ≥ 3 (%)</th>
<th>Placebo (N=151)</th>
<th>Grade ≥ 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruising</td>
<td>23 1 0 15 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 1 0 7 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15 0 0 5 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>9 1 1 0 0 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>5 0 0 1 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frustration</td>
<td>13 1 1 0 2 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12 2 1 5 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 1 1 5 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8 0 3 0 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Acute Graft-Versus-Host Disease: Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild discomfort</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe discomfort</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Critical illness</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Chronic Graft-Versus-Host Disease: Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild to severe</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Critical</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Polycythemia Vera: Selected Laboratory Findings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Acute Graft-Versus-Host Disease: Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild discomfort</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe discomfort</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Critical illness</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Chronic Graft-Versus-Host Disease: Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild to severe</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Critical</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Chronic Graft-Versus-Host Disease: All-Grade Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild to severe</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Critical</td>
<td></td>
</tr>
</tbody>
</table>

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

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Secondary Malignancies: Another JAK inhibitor has increased the risk of lymphoma and other malignancies excluding NHL (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.
of treatment because of thrombocytopenia occurred in < 1% of patients receiving Jakafi and < 1% of patients receiving control regimens. Patients with a platelet count of 100 × 10^9/L to 200 × 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 × 10^9/L (17% versus 7%). Neutropenia in the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides a frequency and severity of chronic lab hematologic abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70.9%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>96.2%</td>
<td>86.7%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>5.2%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Additional Data from the Placebo-Controlled Study

- 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 5% 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 elevation was < 1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Polycythemia Vera in a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy (see Clinical Studies (14.2) in Full Prescribing Information). The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=71)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>15 (21)</td>
<td>10 (14)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>Dizziness*</td>
<td>15 (21)</td>
<td>13 (18)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 (18)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12 (17)</td>
<td>&lt; 1 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15 (21)</td>
<td>13 (18)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (8)</td>
<td>6 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Weight Gain*</td>
<td>8 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infections*</td>
<td>8 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (7)</td>
<td>&lt; 1 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=111)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 (65)</td>
<td>&lt; 1 (&lt; 1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 (24)</td>
<td>&gt; 1 (&gt; 1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (3)</td>
<td>&gt; 1 (&gt; 1)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>35 (32)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 5: Acute Graft-versus-Host Disease: Nonhematologic Adverse Reactions Occurring in ≥ 15% of Patients in the Open-Label, Single Cohort Study

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=71)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections (pathogen not specified)</td>
<td>55 (77)</td>
<td>4 (56)</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>51 (72)</td>
<td>13 (18)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>49 (69)</td>
<td>20 (28)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 (52)</td>
<td>14 (19)</td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>32 (45)</td>
<td>29 (39)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32 (45)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>31 (44)</td>
<td>14 (19)</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>22 (31)</td>
<td>11 (16)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (34)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>23 (32)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Pruritic rash</td>
<td>20 (28)</td>
<td>13 (18)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (22)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*Selected laboratory abnormalities are listed in Table 6 below

Table 6: Acute Graft-versus-Host Disease: Selected Laboratory Abnormalities during treatment with Jakafi are shown in Table 6.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=71)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>75 (53)</td>
<td>45 (31)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75 (53)</td>
<td>61 (43)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 (40)</td>
<td>40 (29)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>48 (34)</td>
<td>8 (6)</td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>48 (34)</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>11 (8)</td>
<td>11 (8)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Jakafi (N=158)</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>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 (37)</td>
<td>20 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>73 (47)</td>
<td>11 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>65 (42)</td>
<td>5 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>61 (40)</td>
<td>6 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated amylase</td>
<td>35 (22)</td>
<td>8 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values of baseline

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=158)</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>
<td></td>
</tr>
<tr>
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<td>58 (37)</td>
<td>20 (13)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>73 (47)</td>
<td>11 (7)</td>
<td></td>
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</tr>
<tr>
<td>Elevated AST</td>
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<td>5 (3)</td>
<td></td>
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<td>Creatinine</td>
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<td>Elevated amylase</td>
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<td>8 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values of baseline

Table 8: Chronic Graft-versus-Host Disease: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment
and effectiveness of Jakafi for treatment of pediatric patients have not been established. 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. 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. 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. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old.

DRUG INTERACTIONS

Strong CYP3A4 Inducers Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Strong CYP3A4 inducers Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information], which may reduce efficacy of Jakafi. Monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Strong CYP3A4 Inducers Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity [see Data]. There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. is known to cause major birth defects in 2% to 4% and miscarriages in 15% to 20% of clinically recognized pregnancies. Data: Animal Data Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30, or 60 mg/kg/day in rats and 10, 30, or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from preconception through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). Lactation Risk Summary No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed child, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (see Data). Because many drugs are secreted in human milk, it is advisable for the nursing mother to avoid breast feeding or discontinue breastfeeding during treatment with Jakafi. Breastfeeding is not recommended in patients with hepatic impairment. 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 with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information].
Lee Reviews Trials Supporting IO/TKI Combinations in Frontline RCC

CASE

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

Lee: The National Comprehensive Cancer Network [NCCN] guidelines have multiple regimens for patients with either intermediate- or poor-risk RCC. They are considered preferred regimens and have category 1 evidence. All these have been randomly assigned against sunitinib [Sutent] as the comparator arm. We have 3 regimens in the tyrosine kinase inhibitor [TKI] plus immunotherapy [IO] category. They include axitinib [Inlyta] plus pembrolizumab [Keytruda], cabozantinib [Cabometyx] plus nivolumab [Opdivo], and lenvatinib [Lenvima] plus pembrolizumab. There is the combination of CTLA-4 and PD-1 inhibitors ipilimumab [Yervoy] plus nivolumab. Also in the preferred category but without category 1 evidence is cabozantinib monotherapy.¹

The disclaimer we always give in advance is, you can't do cross-trial comparisons….All first-line trials for the preferred frontline regimens in RCC had category 1 evidence, and they were all randomly assigned against sunitinib with varying [numbers of patients with] intermediate-, favorable-, and poor-risk disease, but [patients with] intermediate-risk disease were the dominant group. All drugs showed a benefit from an overall survival [OS] standpoint, with hazard ratios that were statistically significant. The combination of ipilimumab/nivolumab had an objective response rate [ORR] in the intent-to-treat population of 39%, and the IO/TKI combinations had an ORR that ranged from 56% to 71%.

The complete response [CR] rate for ipilimumab/nivolumab was 12%, axitinib/pembrolizumab was 10%, cabozantinib/nivolumab was 12%, and lenvatinib/pembrolizumab was 16%. The risk of primary progression of disease was 18% for ipilimumab/nivolumab, 11% for axitinib/pembrolizumab, 6% for cabozantinib/nivolumab, and 5% for lenvatinib/pembrolizumab.² In 2021, there were 2 new IO/TKI combinations. Cabozantinib/nivolumab and lenvatinib/pembrolizumab were subsequently approved for treatment of patients with first-line metastatic RCC.⁶⁺⁷

Targeted Oncology™: What are the recommended frontline regimens for advanced RCC with clear cell histology?

LEE: The National Comprehensive Cancer Network [NCCN] guidelines have multiple regimens for patients with either intermediate- or poor-risk RCC. They are considered preferred regimens and have category 1 evidence. All these have been randomly assigned against sunitinib [Sutent] as the comparator arm. We have 3 regimens in the tyrosine kinase inhibitor [TKI] plus immunotherapy [IO] category. They include axitinib [Inlyta] plus pembrolizumab [Keytruda], cabozantinib [Cabometyx] plus nivolumab [Opdivo], and lenvatinib [Lenvima] plus pembrolizumab. There is the combination of CTLA-4 and PD-1 inhibitors ipilimumab [Yervoy] plus nivolumab. Also in the preferred category but without category 1 evidence is cabozantinib monotherapy.¹

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CASE UPDATE

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

What data support the combination of lenvatinib and pembrolizumab for clear cell RCC?

Lenvatinib/pembrolizumab was FDA approved based on the CLEAR study [NCT02811861], a 3-arm study comparing lenvatinib at 20 mg daily plus pembrolizumab at 200 mg...
IV [intravenous] every 3 weeks vs lenvatinib at 18 mg daily plus everolimus [Afinitor] at 5 mg daily vs sunitinib at 50 mg 4 weeks on, 2 weeks off.

To be eligible for this clinical trial, one had to have advanced RCC, be treatment naïve, and have a KPS of at least 70%, measurable disease, and adequate organ function. Patients were stratified based on geographic region and by MSKCC [Memorial Sloan Kettering Cancer Center] risk categories. The primary end point of this clinical trial was progression-free survival [PFS]. Secondary end points were OS, ORR, safety, and quality of life, and exploratory end points [were] duration of response and some biomarkers. It was a positive study result, and both lenvatinib plus pembrolizumab and lenvatinib plus everolimus ended up showing a statistically significant improvement in PFS, with a hazard ratio for lenvatinib/pembrolizumab of 0.39 [95% CI, 0.32–0.49; \( P < .001 \)] and an increase in median PFS from 9.2 months on sunitinib to about 24 months on lenvatinib/pembrolizumab. The subgroup analyses that were preplanned favored lenvatinib/pembrolizumab over sunitinib, and these included age, sex, geographic location, different risk categories, performance status, the number of sites of disease, and PD-L1 positivity score. The sites of disease also favored the combination, whether patients had bone or liver metastases, prior nephrectomy, and prior sarcomatoid histology. The Kaplan-Meier curves for OS showed an early separation at the 26-month median follow-up, with a hazard ratio for lenvatinib/pembrolizumab of 0.39 [95% CI, 0.32–0.49; \( P < .001 \)] and an increase in median PFS from 9.2 months on sunitinib to about 24 months on lenvatinib/pembrolizumab.

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If you look at the percentage of patients who required some sort of discontinuation of a drug, discontinuation of lenvatinib was about 25% compared with 14% for sunitinib. Discontinuation of pembrolizumab was close to 30%, and discontinuation of both drugs was about 13%. There were higher levels of toxicity with combination therapy, higher levels of diarrhea, a little more hypertension, but relatively low increases in AST [aspartate aminotransferase] and ALT [alanine transaminase] levels and higher levels of proteinuria.

### What are the recommended dosage and dose adjustments for lenvatinib plus pembrolizumab?

The recommended dosage for lenvatinib is 20 mg daily, and pembrolizumab is given at 200 mg every 3 weeks for up to 2 years. At the end of 2 years, lenvatinib is continued as a single agent until either progression or toxicity. The lenvatinib is given as both 4-mg and 10-mg pills. The dose

### Table. Confirmed Objective Response Rate in the CLEAR Trial

<table>
<thead>
<tr>
<th></th>
<th>LENVATINIB PLUS PEMBROLIZUMAB</th>
<th>LENVATINIB PLUS EVEROLIMUS</th>
<th>SUNITINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)</td>
<td>71.0 (66.3–75.7)</td>
<td>53.5 (48.3–58.7)</td>
<td>36.1 (31.2–41.1)</td>
</tr>
<tr>
<td>Complete response (%)</td>
<td>16.1</td>
<td>9.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Partial response (%)</td>
<td>54.9</td>
<td>43.7</td>
<td>31.9</td>
</tr>
<tr>
<td>Stable disease (%)</td>
<td>19.2</td>
<td>33.6</td>
<td>38.1</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>5.4</td>
<td>7.3</td>
<td>14.0</td>
</tr>
<tr>
<td>Unknown or not evaluable (%)</td>
<td>4.5</td>
<td>5.7</td>
<td>11.8</td>
</tr>
</tbody>
</table>
What data led to the approval of nivolumab plus cabozantinib in the frontline advanced RCC setting?

The CheckMate 9ER study [NCT03141177] led to the regulatory approval of cabozantinib plus nivolumab. This was a randomized phase 3 study comparing nivolumab at 240 mg every 2 weeks with cabozantinib at 40 mg daily. Cabozantinib monotherapy is given at 60 mg, so this is already starting with dose reduction of the cabozantinib. This was compared with sunitinib [at] 50 mg on a 4-weeks-on, 2-weeks-off cycle. Enrolled patients with advanced or metastatic RCC had to have at least a clear cell component but [also] any sort of IMDC risk. The primary end point was PFS.4

The primary end point after a median follow-up of 33 months showed early separation of the Kaplan-Meier curves, with a hazard ratio of 0.51 [95% CI, 0.41-0.64; P < .0001]. The median PFS of cabozantinib/nivolumab was 16.6 months vs 8.3 months for sunitinib [HR, 0.56; 95% CI, 0.46-0.68], which reads as a positive clinical trial result.5,11 [The PFS for] all subgroups favored the combination of cabozantinib/nivolumab, including geographic region, different IMDC risk stratification, PD-L1 positivity or negativity, age, sex, performance status, and whether they had bone metastases or prior nephrectomy.4

The OS, a secondary end point, after a median follow-up of 33 months showed early separation of the Kaplan-Meier curves at the first scans or even before.11 The median OS of the population on cabozantinib/nivolumab was 38 months compared with 34 months on sunitinib [HR, 0.70; 95% CI, 0.55-0.90]. At the 24-month landmark, about 70% of patients treated with cabozantinib/nivolumab were alive compared with 60% for sunitinib.

The ORRs favored the combination, with patients having an ORR of 56% with cabozantinib/nivolumab compared with 27% [with] sunitinib.4,11 The CR rate was 8% with cabozantinib/nivolumab and about 5% with sunitinib. This didn’t seem to stratify based on whether they were PD-L1 positive or negative. After longer follow-up, the CRs slowly creep as high as 12% for the combination of cabozantinib/nivolumab. For the safety data, in terms of discontinuation of treatment for either drug, about 44% of patients on cabozantinib/nivolumab discontinued: 27% because of disease progression and about 15% related to toxicity.4,11

About 5% or 6% of patients discontinued either cabozantinib alone or nivolumab alone, and about 3% discontinued both at the same time. Most of the AEs like diarrhea, hand-foot syndrome, and hypertension were similar between cabozantinib and sunitinib. One thing they did notice with cabozantinib/nivolumab at a little higher frequency was a risk of increases in AST and ALT levels.■

REFERENCES

Strategic Alliance Partnership

Targeted Oncology™ has partnered with leading national oncology associations, state oncology societies, and community cancer centers to bring oncologists the most important news in cancer research and the latest in best treatment practices. Scan the QR code to check out our partner page.

September 2022 | Case-Based Roundtable Meetings Spotlight 21
Roundtable Discussion: Considerations of Transplant and JAK Inhibition Guide Treatment for a Patient With Myelofibrosis

CASE SUMMARY

A 68-year-old man presented to his physician with symptoms of fatigue, drenching night sweats, abdominal pain, and intermittent fevers lasting 4 months; he also reported increased bruising. His medical history included type 2 diabetes and atrial fibrillation, both controlled with medication. The spleen was palpable 10 cm below the left costal margin. A CT of the abdomen/pelvis showed splenomegaly with spleen length of 30.3 cm. His ECOG performance status was 2.

A bone marrow biopsy showed a JAK2 V617F mutation, megakaryocyte proliferation and atypia with evidence of reticulin fibrosis (grade 3), and CD34+/CD117+ immunostaining with 1.2% blasts. His cytogenetics were normal. A blood smear revealed leukoerythroblastosis. The patient received a diagnosis of primary myelofibrosis with MIPSS70+ (Mutation and Karyotype-enhanced International Prognostic Scoring System) version 2.0, high-risk status.

DISCUSSION QUESTIONS

• What triggers the initiation of therapy for a patient with myelofibrosis?
• Why is controlling symptoms important?

Test | Values | Reference
--- | --- | ---
Red blood count | $3.40 \times 10^{12}/L$ | 
Hemoglobin | 9.1 g/dL | 13.9-16.3 g/dL
Hematocrit | 36% | 
Mean corpuscular volume | 94 fl | 
White blood count | $19.0 \times 10^9/L$ | 4.5-11 × 10⁹/L
Platelets | $43 \times 10^9/L$ | 150-450 × 10⁹/L

KUYKENDALL: When you’re thinking about a patient with myelofibrosis, what’s the trigger to initiate therapy for a patient like this?

WANG: Symptoms, but it depends on the risk factors. Mainly, if they have B symptoms, or if there’s anemia, splenomegaly, fever, chills, night sweats—anything that warrants treatment, or any high-risk features based on risk stratification.

KUYKENDALL: A lot of [these factors] are not modifying the underlying disease. The goal is to make patients feel better, and sometimes we can do that in different ways. Sometimes that’s spleen enlargement; sometimes it’s constitutional symptoms; sometimes it’s anemia.

What’s the importance to you in controlling symptoms? Is that something that you feel has prognostic value?
**CARTWRIGHT:** The first thing to consider is if the patient is a potential transplant candidate. A lot of patients are, but I always think about that first before deciding anything. Every patient is different. Some patients have a lot of symptoms, mostly with sweats and itching. For some people, the spleen is uncomfortable, so I think it depends on the patient, but controlling symptoms is the most important thing.

**KUYKENDALL:** It’s a good point, as far as transplant goes. I think until we have something that’s truly disease modifying, transplant has to be in the back of our minds for all these patients. That offers curative potential and it’s something that should be brought to the table right off the bat in patients who are transplant candidates who have higher-risk disease, which the majority of these patients do.

### DISCUSSION QUESTIONS

- How important is early initiation of therapy?
  - What is the timing for starting JAK (Janus kinase) inhibitor therapy and how does one decide?
  - How does the nature and burden of symptoms influence the decision to initiate JAK inhibitor therapy?

**KUYKENDALL:** Do you think about the timing of starting a JAK inhibitor? Do you think about getting this on board early in the disease process, or do you ascribe to this idea of not wanting to waste your bullets and...save it until a patient may have more chance of benefitting?

**YELLU:** Usually, I start these medications for symptom burden or when a patient is experiencing worsening cytopenias. We could wait if the patient is asymptomatic or counts are stable, but when they need it, they need it. JAK inhibitors can be used as a bridge for transplant if the patient is eligible for transplant.

**KUYKENDALL:** To build on your point, let’s say you have a patient with myelofibrosis that presents with splenomegaly; you’ve seen it on imaging, maybe, but it’s not causing a ton of symptoms. Is that someone you consider to be a candidate for a JAK inhibitor, if they have moderate splenomegaly but it’s not causing them a lot of trouble?

**YELLU:** Yes and no. We could use a JAK inhibitor in those patients. There is no survival data for JAK2 inhibitors. We could wait, if that’s the patient’s preference to where they want to be, and work with JAK2, or wait until they develop symptoms.

**KUYKENDALL:** I agree. It’s a question we don’t fully know the answer to. We’ll go through some data on ways to think about it going forward, but it’s a challenging question we all struggle with.

We’ve talked about B symptoms or constitutional symptoms, splenomegaly, thrombocytopenia, anemia. Are you typically reaching for JAK inhibitors in the setting of splenomegaly and constitutional symptoms? Are you considering using them for cytopenias as well? What goes into your thought process there?

**DANDAMUDI:** Especially when the patient is cytopenic, it’s challenging. But the main thing is I would try to start JAK2 [inhibition] on a symptom basis; with splenomegaly, early satiety, night sweats, significant quality-of-life issues. Those are the people who I would try to start on JAK2. When there are cytopenias, now with the newer drug available, I would probably start very early.

**KUYKENDALL:** It’s certainly a challenge. Traditionally we’ve been using ruxolitinib [Jakafi], which has various different doses we can use. Are you someone who typically likes to start at a lower dose and see if that works, start low and escalate, or start with a higher dose and taper down if needed?

**DANDAMUDI:** I believe with ruxolitinib, less than 15 mg may not be helpful in myelofibrosis; so the higher the dose, the better it is. That’s why I’m very pleased to have the new drug. For cytopenic patients, pacritinib [Vonjo] would be a good option to think about.

**KUYKENDALL:** Definitely.

### DISCUSSION QUESTIONS

- What are the goals of therapy for this kind of patient?
- How are treatment options discussed with patients?
- When is clinical trial enrollment considered?

**YELLU:** This is a patient presenting with constitutional symptoms, cytopenias, and splenomegaly. The patient is symptomatic. He may be a candidate for a JAK2 inhibitor. He may be a candidate for transplant, but given the performance status of 2, I’m not sure whether he would be eligible for transplant. I think this is going to be more symptom reduction and helping cytopenias, so I would start treatment with a JAK2 [inhibitor].
KUYKENDALL: With the big spleen and the symptoms, that seems to be dominating the picture. I think we could all make the case that hypothetically, with the splenomegaly and the symptoms, the patient could benefit from a JAK inhibitor. How would you go about addressing these cytopenias? He's got pretty marked thrombocytopenia here at 43 × 10^9/L.

KALMAN: If all you had was the ruxolitinib—which we don’t have—then you would have to start at very low doses. But now, I would start with pacritinib.

KUYKENDALL: That’s certainly a timely suggestion, given the recent approval. I think that this would be a patient in whom one would be hard pressed to get a decent response to ruxolitinib, given his platelet counts.

You had mentioned the potential for transplant. This is a 68-year-old with high-risk disease and thrombocytopenia. How do you have that discussion, when you’re talking to him about potential transplant vs a JAK inhibitor?

CARTWRIGHT: The criteria for who’s eligible for transplant is constantly evolving. We used to say, “don’t [give a] transplant [to] people over 70 years old,” but that doesn’t seem to be the case anymore. A patient like this seems borderline for transplant, so I would discuss that as an option with him and refer him to see if he may or may not be a candidate. But you also have to tell him the medication isn’t going to cure things; it’s just going to control [the] symptoms.

This patient is 68 years old. He seems in reasonably good health. Half the 68-year-olds have type 2 diabetes, so it’s not a big deal, especially if it’s controlled. With a patient like this, I’m not absolutely sure what I’d do right off the bat, but I’d probably refer him for at least transplant. It’s hard to do clinical trials for rare conditions in private practice. You don’t see these patients that often.

For a patient like this, I’d probably…see if he’s a candidate for transplant and if there’s a clinical trial that I’m not aware of. It’s not like acute myeloid leukemia [where] they have to be started on treatment tomorrow. We have some time. Not only that, but a lot of patients also request second opinions anyway.

KUYKENDALL: That’s a great answer. When I talk to patients like this, we could do 2 things—transplant is certainly a curative option. I agree with you, this does seem like a borderline patient, but at the same time they might be someone whose performance status improves if they get treatment for their disease.

Who am I to say that they aren’t someone who might be motivated to go through [treatment] and get a curative approach? This might be someone who has their sights set on living another 20 or 30 years. I think a lot of this comes down to patient motivation, patient interest, health, transplant status, and donor availability. But I think from a disease standpoint, certainly that warrants a transplant consideration.

You touched on clinical trials. This is certainly a subject near and dear to my heart. Right now there are a ton of clinical trials for myelofibrosis, [though] not out in the community most of the time. Most of the time they’re at centers where a lot of these patients are being seen. Currently there are 11 phase 3 clinical trials for patients with myelofibrosis, all of which are expecting to enroll hundreds of patients, which is going to be a challenge. None of them have what I would consider to be curative intent, but they’re hoping to either broaden the treatment options for myelofibrosis or do something better than we’re currently doing. So, what would be an indication for you to refer a patient with myelofibrosis for a clinical trial?

WANG: I think if the patient’s performance status is good and there are no good available options, or if the patient is willing. I personally don’t do clinical trials [at my practice], but a clinical trial is never the wrong answer. I would assess performance status, look at the availability of clinical trials, and talk to the patient. If the patient is willing, screen them for clinical trials.

GLICK: Even if we agree that this patient should be evaluated at least at a tertiary care center for a transplant, is there any role for trying to reduce his spleen size [before-hand] or in the meantime while that’s being organized?

KUYKENDALL: Absolutely. I think the 2 are mutually exclusive. Transplant doesn’t happen tomorrow, and a lot of the features of this patient’s disease make him…a poor transplant candidate. They may be able to be improved with treatment. Splenomegaly sometimes delays engraftment and creates a problem from that standpoint when patients go into [receiving a] transplant with significant splenomegaly.

We can improve splenomegaly with a JAK inhibitor. Constitutional symptoms can certainly depress someone’s performance status. They can worsen their albumin [and] nutritional status, and that’s going to be a difficult transplant candidate. There have been several studies talking about timing of [the] transplant, how that’s done by bridging with JAK inhibitors. What we found from [the data from] those studies is it’s safe to do; it’s safe to treat with JAK inhibitors prior to transplant. Often it makes them a better transplant candidate.

The question is, how do you take them off [the inhibitors]? I think that’s the question the transplanters are asking. Do you taper them off right before transplant? Do you continue into the peritransplant period and taper off...
early in the transplant process? We run into problems with ruxolitinib discontinuation because it can cause cytokine release syndrome and rapid growth of the spleen when you take patients off.

Recently there have been intriguing safety data that confirm it’s safe to continue ruxolitinib early in the transplant process and try to take patients off sometime during that first month. It’s now complicated by the fact that ruxolitinib is approved for chronic graft-vs-host disease, so maybe it has a role in that process as well, but it does cause cytopenias.

**POLLING QUESTION**

“The patient is referred for evaluation for autologous stem cell transplant. In the meantime, what are you most likely to recommend as a potential bridging therapy?”

- Initiate pacritinib: 73% (8) votes
- Initiate fedratinib: 18% (2) votes
- Initiate ruxolitinib: 9% (1) votes
- Observation: 0% (0) votes
- Clinical trial: 0% (0) votes

**Total votes: 11**

**KUYKENDALL:** This goes back to the point that maybe there’s a role for JAK inhibition here. We’re talking about a patient with thrombocytopenia, big spleen symptoms. We have a lot of people that are up with the literature feeling very confident in prescribing pacritinib hot off the press. We do have votes for fedratinib [Inrebic]; I think it’s an interesting decision and certainly reasonable. Does someone want to explain why they’d reach for what they voted for in the poll?

**WERTHEIM:** I chose pacritinib because the platelets were under $50 \times 10^9$ /L.

**DANDAMUDI:** I picked pacritinib too because of the platelets. That’s my favorite option right now.

**KALMAN:** I voted for pacritinib. The thing about pacritinib is how good it is [at reducing] symptoms. I think I would go with the labeled drug.

**DISCUSSION QUESTION**

What is your experience with using pacritinib and fedratinib?

**KUYKENDALL:** Do you have experience using pacritinib in the clinic, including seeing a patient who is on a clinical trial?

**KHAN:** I’ve used it. I have a patient that was transferred to me from a tertiary care center, and he was already on it, so I’ve been following him. He’s on pacritinib 200 mg twice daily. I haven’t had any issues thus far. I guess you have to watch the kidney functions. He has stage III kidney disease, but his kidney functions have been stable.

**KUYKENDALL:** This is a drug that’s been utilized in several clinical trials, so the chances of someone being seen in the community who’s been on it is not uncommon, given the development that it’s gone through.

Does anyone want to chime in with their experience with fedratinib? Have you used it? Has the gastrointestinal [GI] toxicity been difficult?

**AMIN:** I have used it. There was some GI toxicity, but overall it was manageable. I used it in the second-line setting, in a total of 3 patients, because fedratinib has data [in both first and second line]. I use ruxolitinib for first-line [treatment]. Also, the patients were already on ruxolitinib before the drug was approved in both conditions. It gave some additional time for these patients. Ultimately, 2 of the patients passed away and 1 patient is still OK.

**KUYKENDALL:** You didn’t think the GI toxicity was overly challenging?

**AMIN:** No. Overall, the disease at that point is more challenging than the GI toxicity per se. They became transfusion dependent, but the drug helped reduce transfusion dependency because of some improvement in spleen size. But I didn’t see GI toxicity as challenging overall, I just think the disease was quite symptomatic that time.

**KALMAN:** I used fedratinib in 1 or 2 patients. It can work for some period of time in people who fail ruxolitinib, or there are some people who are intolerant of ruxolitinib. I think it’s good to have different options for these patients. You have to watch the thiamine levels with this drug. It was good to have for people whom, for one reason or another, I wanted to get off ruxolitinib.

**KUYKENDALL:** My experience has been that it’s hard to find the right patient for fedratinib. But having used it in maybe a dozen or so patients, I think the GI toxicity has not been overly concerning to me—at least with prophylactic antiemetics; counseling patients; knowing that it can cause loose stools, diarrhea, and advising [patients about] the high-fat meal to take it with. That was not what I expected when it first got approved, because some of these studies were done concurrently with ruxolitinib. The GI toxicity was something that was reported in a lot of these patients.
Case-Based Roundtable Meetings Spotlight

MYELOPROLIFERATIVE NEOPLASMS

FROM THE DATA

In the PERSIST-2 trial (NCT02055781), 311 patients with myelofibrosis and thrombocytopenia were randomly assigned 1:1:1 to pacritinib (Vonjo) at 200 mg twice daily or 400 mg once daily vs best available therapy (BAT).3 Spleen volume reduction (SVR) of 35% or more was seen in 18% of patients who received pacritinib compared with 3% of patients who received BAT ($P = .08$) in the intention-to-treat population. Pacritinib twice daily showed significant improvement in SVR and total symptom score (TSS) vs BAT ($\geq 35\%$ SVR in 22% vs 3%, respectively [$P = .001$]; $\geq 50\%$ reduction in TSS in 32% vs 14%, respectively [$P = .01$]).

AMIN: I never start up front at 400 mg daily, although there is always an urgency where I escalate the drug dose over a period of 2 to 4 weeks.

KUYKENDALL: That’s interesting. I typically start with 400 mg and then dose reduce, but [it’s] interesting to hear the practice of starting low and escalating.

DISCUSSION QUESTIONS

• What are your reactions to the data from the PERSIST-1 (NCT01773187) and PERSIST-2 (NCT02055781) trials?2,3
• How should patients be counseled about receiving pacritinib?

GLICK: It’s pretty exciting to have a new drug available to treat this rare disease, especially for the patients who have low platelet counts or who have failed ruxolitinib. There’s a new option for them.

KALMAN: I would definitely use it for somebody who has less than $50 \times 10^9/L$ platelets, which is the label of the drug. Otherwise I think it will probably be third line unless you can use it in the first line, but I don’t know if you can get it paid for first line. It’s probably less than $50 \times 10^9/L$ [in the first line], or second or third line.

KUYKENDALL: The data for the thrombocytopenic patients are remarkable and we don’t have too many options there [From the Data]. The question is where does this fit otherwise, in patients who don’t have marked thrombocytopenia? Seeing GI toxicity with pacritinib, and similarly what we see with fedratinib, how do you counsel patients on a drug that may make them have significant diarrhea, nausea, and vomiting?

DANDAMUDI: I would proactively prescribe antiemetics to make sure that the patient doesn’t have nausea and all this. I would also discuss about the diarrhea, using maybe loperamide [Imodium] or starting loperamide early rather than waiting, and see how he does. If it continues to be refractory, then I need to look into the dose adjustments and take it from there.

KUYKENDALL: What goes into your thought process as far as when to use a JAK inhibitor and which agent to use? What’s going to be the most important thing?

MAKONI: I’d look at thrombocytopenia and I would consider pacritinib for platelets less than $50 \times 10^9/L$.

KUYKENDALL: Does the nature of the symptoms come into play? We looked at how this impacts symptoms. Is that going to affect your specific JAK inhibitor or is it going to affect the dose of your JAK inhibitor? What if someone has a lot of constitutional symptoms but not a lot of spleen enlargement or spleen symptoms?

MAKONI: I would use JAK inhibitors for someone with constitutional symptoms and particularly pacritinib if you have a lot of constitutional symptoms.

KUYKENDALL: What about convenience or logistics? These are expensive medications. What’s been people’s experience in getting these drugs paid for and approved—has it been an easy process or difficult process?

AMIN: We have health maintenance organization [HMO] insurance in quite a significant amount in Florida, so there’s a battle, but it usually gets approved because it’s an FDA label. These agents are very expensive agents compared with any other targeted oral therapy. But ruxolitinib, pacritinib, and fedratinib are pretty much the same price. We choose [based]
more on the clinical indication, but for price, they’re all pretty much comparable. Co-payment is especially an issue with the HMO patients.

**KUYKENDALL:** I’ll give you a hypothetical: What if one of these was a lot cheaper than the others; are the data strong enough? Let’s say fedratinib or pacritinib was a lot cheaper than ruxolitinib, would you still prefer to use ruxolitinib in those patients, or would you consider an alternative based on cost alone?

**AMIN:** No; then we’ll consider the cheaper drug. There’s no comparison, but looking at the data, it’s more or less going to fall into the same category. In fact, fedratinib has an indication in the second line and first line, and pacritinib works even in low platelets. If the cost is important, then go with the drug that is cheaper. I think it’s more rational too, economical. We have to consider financial toxicity. These drugs are very expensive though; the price of ruxolitinib is outrageous.

**KUYKENDALL:** It’s an interesting question. Unfortunately, they’re all very expensive so it’s not one that’s a true question; it’s more hypothetical at this point.

**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.¹³

**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 medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute medical management as needed.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**
After a median ~30 months of follow-up, response rates were not reached with DARZALEX® + Rd vs 31.9 months with Rd alone.¹, ⁴

- 70.6% of patients had not progressed with Rd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3).¹

**Demonstrated safety profile**

- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia

- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%).

**MAIA Study Design:** A phase 3, global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.¹

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (D); HR=hazard ratio; IRR=Injection-related reaction; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (D).

**Efficacy results in long-term follow-up**

- At median ~5 years (56 months) of follow-up, response rates were not reached with Rd vs 34.4 months with Rd alone.²

- 53% of patients had not progressed after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35).¹

**Safety results in long-term follow-up**

- At median ~5 years of follow-up (median treatment duration of 47.5 months)²:
  - Most frequent TEAEs: 30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms
  - Grade 3/4 infections were 41% for DRd vs 29% for Rd
  - Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

With an ~3 to 5 minute subcutaneous injection, DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.², ⁵, ¹¹

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**Powerful efficacy to start the treatment journey**

- For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

- For patients with a history of chronic obstructive pulmonary disease (COPD), consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids and for patients with chronic obstructive pulmonary disease.

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

**DARZALEX FASPRO®: Hypersensitivity and Other Administration Reactions**

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

**Systemic Reactions**

- In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%), Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. 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 appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

**SAFETY INFORMATION CONTINUES ON NEXT PAGE**
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 initiation of the administration of DARZALEX FASPRO®] or administration-related reactions.

OCULAR ADVERSE REACTIONS, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions, with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX 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 the 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 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, diarrea, 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.


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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, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX 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 hyaluronic acid-fihj) is indicated for the treatment of adult patients with multiple myeloma:

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

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.
DARZALEX® (daratumumab) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation [see Warnings and Precautions].

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported [see Adverse Reactions].

In clinical trials (monotherapy and combination: N=2,060), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to 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 4/5) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUEULES, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 13% 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 symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [see References]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions]. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX [see Dosage and Administration (2.1) in Full Prescribing Information].

Neutropenia

DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions]. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia

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

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected in serum. A 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.

Embry-Fetal Toxicity

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

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

ADVERSE REACTIONS

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

- Infusion-related reactions [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

Clinical Trials Experience

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the 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 were neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.64 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).
Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Rd (N=365)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
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<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>0</td>
<td>46</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>41</td>
<td>1</td>
<td>&lt;1</td>
<td>36</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>&lt;1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Upper respiratory tract infectiona</td>
<td>52</td>
<td>2</td>
<td>&lt;1</td>
<td>36</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchitisb</td>
<td>29</td>
<td>3</td>
<td>0</td>
<td>21</td>
<td>1</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Pneumoniaca</td>
<td>26</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Infusion-related reactionsb</td>
<td>41</td>
<td>2</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>41</td>
<td>2</td>
<td>0</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
<td>0</td>
<td>28</td>
<td>4</td>
<td>0</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>3</td>
<td>&lt;1</td>
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<tr>
<td></td>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
<td>0</td>
<td>18</td>
<td>2</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Chills</td>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>34</td>
<td>3</td>
<td>&lt;1</td>
<td>26</td>
<td>3</td>
<td>&lt;1</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Muscle spasms</td>
<td>29</td>
<td>1</td>
<td>0</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnear</td>
<td>32</td>
<td>3</td>
<td>&lt;1</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>30</td>
<td>&lt;1</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperglycemiac</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypocalcemiac</td>
<td>14</td>
<td>1</td>
<td>&lt;1</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertensiaca</td>
<td>13</td>
<td>6</td>
<td>&lt;1</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: DRd=daratumumab, Rd=lanalidomide-dexamethasone.

a. Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis.

b. Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis.

c. Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcocal, Pneumonia viral, Pulmonary mycosis.

d. Infusion-related reaction includes terms determined by investigators to be related to infusion.

e. Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling.

f. Cough, Productive cough.

g. Blood pressure increased, Hypertension.

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Rd (N=365)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
<td>3</td>
<td>58</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>61</td>
<td>39</td>
<td>17</td>
<td>77</td>
<td>28</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>84</td>
<td>41</td>
<td>11</td>
<td>75</td>
<td>36</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>47</td>
<td>13</td>
<td>0</td>
<td>57</td>
<td>24</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Key: DRd=daratumumab, Rd=lanalidomide-dexamethasone.

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX (see Clinical Studies (14.2) in Full Prescribing Information). Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd). Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% higher incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

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

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>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Rd (N=281)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
<td>0</td>
<td>25</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnear</td>
<td>21</td>
<td>&lt;1</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Muscle spasms</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: DRd=daratumumab, Rd=lanalidomide-dexamethasone.

a. upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinustis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection.

b. Infusion-related reaction includes terms determined by investigators to be related to infusion.

c. Cough, productive cough, allergic cough.

d. Dyspnea, Dyspnea exertional.

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.
Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th></th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</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.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

Grade 3 or 4 infections were reported as follows:
- a where carfilzomib 20/56 mg/m² was administered twice-weekly
- b where carfilzomib 20/70 mg/m² was administered once-weekly
- a where carfilzomib 20/56 mg/m² was administered twice-weekly
- b where carfilzomib 20/70 mg/m² was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; D-Rd: 2%, Rd: 2%; D-Vd: 0%, Vd: 0%
- Fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

Immunogenicity

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

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,383 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Postmarketing Experience

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

Immune System disorders: Anaphylactic reaction, IRR (including deaths)
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

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 dithiotreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial 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. Refer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 null) were found to have reduced reproductive potential.

Thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional information. The combination of DARZALEX and lenalidomide, pomalidomide, or 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 for additional information on use during pregnancy.

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 circulation 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, cough, 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].

Embryofetal 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 and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, pomalidomide, or thalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program [see Use in Specific Populations].

Hereditary Fructose Intolerance (HFI)
DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol [see Description (11) in Full Prescribing Information].

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
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cp-271933v2
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

In a pooled safety population of 888 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 8% with the second injection and dexamethasone, and 4% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days).

Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients. Severe reactions, including hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

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

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, melphalan and dexamethasone [see Adverse Reactions]. Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class III or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIb or IV dyspnea 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.

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause deplletion 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 Anti-glubulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect anti-glubulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References (15)].

The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

Neutropenia

DARZALEX FASPRO is associated with neutropenia; dose modifications and discontinuation of DARZALEX FASPRO may be considered in patients with neutropenia for signs of infection. Neutropenia was observed in >5% of patients, including Grade 3 reactions in 1.7% and Grade 4 reactions in 0.7%.

Thrombocytopenia

DARZALEX FASPRO is associated with thrombocytopenia, which may result in the discontinuation of DARZALEX FASPRO. Thrombocytopenia was observed in >5% of patients, including Grade 3 reactions in 2.4% and Grade 4 reactions in 0.4%.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

### Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Deskcontinued (N=65)</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>52</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionb</td>
<td>43</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>23</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Bronchitisc</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

a Fatigue includes asthenia, and fatigue.  
b Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.  
c Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.  
d Bronchitis includes bronchitis, and bronchitis viral.  
e Dyspnea includes dyspnea, and dyspnea exertional.  
f Cough includes cough, and productive cough.  
g Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

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

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Deskcontinued (N=65)</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
<td></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 hematologic 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 circulation 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, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

**REFERENCES**

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

**Hypersensitivity and Other Administration Reactions**
Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, 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].

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Victor Gian, MD
Ryan Carr, MD
Jewraj Maheshwari, MD,
Emmanuel Nidhiry, MD
Michel E. Kuzur, MD
Zuhair Ghanem, MD
Carl R. Willis, MD
Venu Madhav Konala, MD
Muhammad-Ali Zaydan, MD
Michael P. Hemphill, MD

Event region: Tennessee/Kentucky

Roundtable Discussion: Hamilton Compares Therapy Options and Sequencing for Recurrent TNBC

CASE SUMMARY
A 48-year-old woman with T1N1 triple-negative breast cancer (TNBC) received adjuvant dose-dense doxorubicin and cyclophosphamide (AC) plus paclitaxel, which she tolerated well. Eight months after completion of adjuvant therapy, she reported worsening fatigue.

Laboratory results:
- Alanine aminotransferase: 1.5 times upper limit of normal (ULN)
- Aspartate aminotransferase: 1.5 times ULN

A CT scan showed 1 liver and 2 left lung lesions, and biopsy of the liver lesion confirmed recurrent metastatic TNBC. A brain MRI was negative for brain metastasis. Genetic panel testing was negative for detectable mutations; PD-L1 expression on immune cells (Ventana SP142 assay) was 0%. The patient had no significant comorbidities and was otherwise healthy, with an ECOG performance status of 0.

POLLING QUESTION
“What therapy would you recommend for metastatic recurrence of triple-negative breast cancer, 8 months after adjuvant dose-dense doxorubicin and cyclophosphamide plus paclitaxel?”

- IV single-agent chemotherapy: 69% (9)
- Oral single-agent chemotherapy: 23% (3)
- Combination chemotherapy: 8% (1)
- Clinical trial: 0% (0)
- Other: 0% (0)

Total votes: 13

KHASAWNEH: There is no wrong answer here, [in my opinion]. TNBC is definitely an orphan disease; survival is lowest among all breast cancer categories. She progressed 8 months after adjuvant dose-dense AC followed by paclitaxel. She’s definitely in trouble, and most likely she’ll succumb to her disease, given her young age. The best option for her, in my opinion, would be to enroll in a clinical trial because all other options can be given through standard of care, but a clinical trial would be the best option to try to explore any novel agents, or a novel combination of the approved agents on the market.

HAMILTON: Yes. Anybody else want to weigh in?

CARR: I was going to say the same thing that Dr Khasawneh said. This is a young woman with recent adjuvant therapy who relapsed early—a clinical trial is what we would do.
HAMILTON: Yes, exactly. I would definitely do a clinical trial too. I don’t tend to use a lot of combination chemotherapy, but this patient relapsed pretty quickly, 8 months after her AC to paclitaxel. So I think I may be leaning toward a combination, gemcitabine [Gemzar] and carboplatin or something like that. But then, at the same time, she has pretty low burden of disease. She has only 2 small lung lesions and 1 liver lesion. I think an IV single agent would be appropriate. But I agree, especially for our patients with TNBC, where iterative care is just not ideal, I’m thinking of a clinical trial.

MAHESHWARI: Yes, I think in a case like this, whatever we do, survival for the next year is very limited. If somebody failed AC followed by paclitaxel, [her chance of survival is poor].

HAMILTON: Right. I agree. She got 3 great chemotherapy agents, and she’s progressing afterward. You don’t have much hope that the fourth is the miracle one.

MAHESHWARI: Yes. Thank you.

POLLING QUESTION
“What therapy would you recommend for metastatic recurrence of TNBC, 24 months after adjuvant dose-dense doxorubicin and cyclophosphamide plus paclitaxel?”
- IV single-agent chemotherapy 71% (5)
- Clinical trial 29% (2)
- Oral single-agent chemotherapy 0% (0)
- Combination chemotherapy 0% (0)
- Other 0% (0)
Total votes: 7

DISCUSSION QUESTION
What single-agent chemotherapy would you give the patient considering this alternate scenario?

HAMILTON: With a bit more indolent disease, I’d probably think about single-agent chemotherapy and not pulling out combination chemotherapy at this time. What regimen would you pick? What chemotherapy, single agent, would you give her if you had to pick at this point? Would you recycle a taxane? Would you do something else?

NIDHIRY: I would probably do a single-agent taxane, like paclitaxel with albumin [Abraxane], or probably carboplatin.

HAMILTON: Does anyone else want to weigh in on what they might pick if it weren’t a clinical trial?

KUZUR: Eribulin [Halaven].

GIAN: Yes. That’s what I was going to say, eribulin.

KUZUR: There’s also the new drug, sacituzumab [Trodelvy], as well?

HAMILTON: Yes, with sacituzumab govitecan we often have trouble getting it reimbursed for the first line because it’s approved for the second line and beyond. Same with eribulin, actually. Sometimes if patients have had neoadjuvant [or] adjuvant chemotherapy, you can give sacituzumab if they relapse quickly, but I don’t know that we’d get it through insurance here with the 24-month gap.

KUZUR: These patients [with TNBC] always make me nervous. They are young, and they’re going to [have potentially poorer results], regardless of anything we do. That’s why I believe in a clinical trial.

HAMILTON: Yes, absolutely.

CASE UPDATE
The patient received frontline gemcitabine plus carboplatin with a documented partial response (PR) lasting 6 months. After 6 months of therapy, she reported worsening fatigue. Disease progression and new metastasis in the liver were discovered. She now had an ECOG performance status of 1.

HAMILTON: [For] the patient with recurrence 8 months after receiving adjuvant dose-dense AC-paclitaxel, what do we recommend as second-line therapy for this patient with metastatic [TNBC]? She got dose-dense AC to paclitaxel, [her disease] relapsed in 8 months, and she got gemcitabine and carboplatin. What’s your next choice?

POLLING QUESTION
“What do you recommend as second-line therapy for this patient’s metastatic TNBC?”
- Sacituzumab govitecan 73% (8)
- Microtubule inhibitor (eribulin, vinorelbine) 27% (3)
- Anthracycline 0% (0)
- Antimetabolite (capecitabine) 0% (0)
- Platinum agent 0% (0)
- Clinical trial/other 0% (0)
Total votes: 11
**GIAN:** I would go ahead with the eribulin at that point, if she couldn’t get on a clinical trial.

**HAMILTON:** A lot of you picked sacituzumab. What’s your experience there?

**CARR:** I haven’t given it yet, but I know it’s an antibody-drug conjugate, and that’s kind of a hot topic. The alternative options are not that appealing; other than eribulin, which we probably won’t get too much out of either in this scenario. I think that’s by default where I was headed.

**HAMILTON:** Has anybody else used sacituzumab?

**GHANEM:** I have used it a couple of times and have had a good experience with it. It is a well-tolerated treatment. The problem with these patients [with recurrent TNBC] is [they have] very aggressive disease. Both of them did well, actually. I don’t recall the response rate that I got in these 2 cases. One of them responded well; the other one had very aggressive disease. She progressed clinically even before I did scans, and then I had to switch again.

**HAMILTON:** Has anybody else used sacituzumab?

**CARR:** I chose a platinum agent. If I recall, this patient has pretty low-volume disease, and this would be second line, and she’s triple negative; so I thought maybe some platinum agent might be useful here to drag things along a little bit, and save the sacituzumab for later on.

**NIDHIRY:** I chose platinum as well, for similar reasons. Because the patient seemed to be responding to chemotherapy, I thought it was reasonable to use that. I thought sacituzumab was approved as a third-line agent, if I’m not mistaken.

**HAMILTON:** You’re right, the clinical trial was third line. What about those of you who picked sacituzumab?

**WILLIS:** I probably would have thought about sacituzumab. Isn’t it second line now?

**HAMILTON:** It is, yes. They expanded the indication; it now has approval for second line.3,4

**KONALA:** She received different agents with chemotherapy; she had AC and dose-dense paclitaxel. It could be good to use a different mechanism of action. It has been proven in the second- and third-line settings, so I chose sacituzumab. We can use carboplatin anytime.

**HAMILTON:** That’s a good point.

### DISCUSSION QUESTIONS

- Regarding 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 to be the ideal therapeutic sequence for PD-L1–negative, BRCA-negative metastatic TNBC?

**HAMILTON:** [We are discussing] the patient with metastatic recurrence 8 months after the dose-dense AC to paclitaxel, who got first-line gemcitabine and carboplatin, had the partial response lasting 6 months, and now has new liver metastases.
What do you think when you’re trying to sequence agents? What goes into your thinking there? Are you thinking about the long haul and tolerability, or are you thinking about what is different that the patient hasn’t seen? How are you choosing what agents you give, and what sequence? I think it’s an important question.

**WILLIS:** I think a lot of it depends on what your molecular studies show you. At some point in the metastatic setting, we probably would have done a panel and found something that we hope we can target. So if *BRCA1* or *BRCA2* are positive, or *PALB2*, then we might consider looking at a PARP inhibitor. If they’re PD-L1 positive or high, you’d maybe think about some type of agent with a PD-L1 inhibitor somewhere in there. And outside that, if you haven’t used sacituzumab, that might be the point [to use it]. And of course, always, you consider clinical trials that might be in the area too.

**HAMILTON:** Yes, I think that’s great. So, Dr Willis, let’s assume that this patient [has] *BRCA* wild-type and PD-L1–negative [disease]. How would you sequence? Let’s say she gets gemcitabine and carboplatin first. What are you thinking about for the second [and third lines]?  

**WILLIS:** If she gets gemcitabine and carboplatin first, I’m thinking about sacituzumab if I haven’t used it already. Then after that, a lot of it depends on the patient’s performance status, and I’d be looking at possibly capecitabine. That’s about all I have left.

**ZAYDAN:** [The first thought that comes to mind] is to consider something that has a different mechanism of action….And second, her current situation, her previous toxicity, and the toxicity of the drug I’m going to use. For example, sacituzumab [can cause] severe neutropenia. Now, if she had a history of neutropenia, or if she has a history of diarrhea, I would be very concerned.

**HAMILTON:** If she were getting gemcitabine and carboplatin first, what would be your second-and third-line picks?

**ZAYDAN:** At this point, I would choose eribulin or vinorelbine. I have used vinorelbine and had some success with it.

**KONALA:** This patient has [had recurrence] after 8 months off chemotherapy. We discussed a clinical trial as a good option. There are some trials combining sacituzumab with immunotherapy. If I can get her on that trial, I would consider that.

**HAMILTON:** So that’s second line?

**KONALA:** Yes.

**HAMILTON:** What would you give third line, after sacituzumab?

**KONALA:** I would probably go back to chemotherapy.

**HAMILTON:** What’s your chemotherapy of choice?

**KONALA:** She already received gemcitabine and carboplatin. We have to try a different mechanism; I’m thinking capecitabine or eribulin after that. I’m hoping we’ll get a different antibody-drug conjugate as we are getting in other cancers.

**NIDHIRY:** I’d probably go with sacituzumab as a second-line therapy because the patient is progressing on the chemotherapy treatments. And if they progress further, probably a clinical trial or maybe something like eribulin.

**GAIN:** At every stage, I would try to put them on a clinical trial first because I don’t think it matters what you use. For second-line therapy, I think you have to look up at how [frail] the patient is as well. If the patient is [frail] and their performance status is down, then you probably want your most active drug second; that would be the sacituzumab. Then you could save other agents such as vinorelbine or eribulin or capecitabine after that. Because they may not get to it, and you want to go with whatever you have that has the best chance of working.

If they have great performance status, feel great, and are doing well, you could try [an agent like sacituzumab]. If it’s been a longer remission, [such as] 24 months, you could try something milder, such as eribulin, and then save sacituzumab for third-line therapy.

**KHASAWNEH:** I agree with all my colleagues. There aren’t set-in-stone guidelines for which one to use. I think it’s a clinical decision, a joint discussion with the patient. But something I always look at is whether there are any residual adverse events [AEs] from previous regimens, like neuropathy.

There is the performance status, the fatigue, the degree of myelosuppression, and the current blood counts. If their blood counts are low, I try not to use a very myelosuppressive regimen, or I start at 75% of the original dose, especially for microtubule inhibitors. And neuropathy is tough to deal with, especially if you’re starting sacituzumab or microtubule inhibitors.

I at least have a discussion with the patient that these things can get worse with the agents I’m going to use, subsequently. But I agree with all my colleagues. I don’t think there are set guidelines for which agent you can use. It’s a shared decision.
**Case-Based Roundtable Meetings Spotlight**

**BREAST CANCER**

**HAMILTON**: Yes, you’re absolutely right; compared with HER2-positive disease, where we have things pretty well scripted, in TNBC, there’s not even 1 standard of care in the first-line space. We cycle through regimens.

**KUZUR**: Sometimes I recycle the paclitaxel, especially if it’s been 2 years or more, and I find the weekly paclitaxel single agent can still give some benefit after you’ve run through the other agents.

**DISCUSSION QUESTIONS**

- What is your experience with efficacy and tolerability of sacituzumab?
- How do you counsel patients regarding sacituzumab?

**HAMILTON**: What is your experience in terms of tolerability? Do you find the diarrhea hard to manage, easier than with the TKIs [tyrosine kinase inhibitors]? How are you counseling your patients about this drug?

**KHASAWNEH**: I thought the diarrhea is easier to control compared with [what] larotinib [causes], for example; just loperamide [Imodium], maximum 8 pills per day, and diphenoxylate and atropine [Lomotil] were sufficient to get the patient through. Fatigue and neutropenic fever were bothersome and disturbing in one patient I had. But she was able to get about 8 months before progressing.

**DISCUSSION QUESTIONS**

- What are your thoughts on the outcomes of the phase 3 ASCENT trial in the context of other therapies that have been most commonly used in the setting of relapsed/refractory mTNBC?
- Have you used sacituzumab govitecan in the second-line metastatic setting? Would you use it earlier than in the third line?
- What is your overall approach to molecular testing at metastatic relapse/progression?
- Have we learned anything about the value of potential biomarkers to guide use of this agent (eg, Trop-2 expression, germline BRCA1/2 mutation status)?
- What therapies did patients randomly assigned to the comparator arm receive? How does that inform how you use sacituzumab govitecan vs other options?

**HAMILTON**: Good to hear. I do something similar. I don’t necessarily have a one-size-fits-all [approach]. I’ve been successful with some patients with mildly low counts, getting away with the “day 1 goes fine, get to day 8, give day 8, and then give pegfilgrastim.” And then patients’ counts are OK by day 21 and the start of the new cycle.

And then, for other patients who have struggled, it’s tough. Because with filgrastim, most often, we can’t get coverage for patients to do that at home, and nobody wants to drive back to the clinic for multiple days of filgrastim. So sometimes I’ve used a dose reduction there with some success.

I think you can pair things. I agree about the diarrhea. I’ve had one patient who had bad diarrhea and a handful of others who have had very minimal to not much diarrhea. I’ve got some patients who have no diarrhea at all. Other patients take 1 loperamide in the morning and they’re good, which is not that much of a crimp on their lifestyle.

**WILLIS**: Yes, I did get a chance to get pegfilgrastim approved, but I gave it after day 8, and she did just fine. In other cases, I did a dose modification and decreased the dose level by 1 step, and I was able to continue it without any problems.

**GHANEM**: For the diarrhea, it’s usually well managed with antidiarrhea medications; it’s not an issue, not like [what we see with] everolimus [Afinitor] or other chemotherapeutics that we use. So, to me, both patients [I treated with sacituzumab] did well.

[Regarding] the neutropenia, both of these patients were third line and already [had] pancytopenia on starting this treatment. I used to bring them early in the week and do the complete blood count. If the patient [had pancytopenia], I gave filgrastim. For most of these patients, by the end of the week, I was able to give the chemotherapy. It’s more of an issue if it’s given later vs in the second line. My experience was good, and [sacituzumab] was very well tolerated.
In the phase 3 ASCENT trial of sacituzumab govitecan, the median progression-free survival was 5.6 months (95% CI, 4.6-6.3) vs 1.7 months (95% CI, 1.5-2.6) with physician’s choice of chemotherapy (HR, 0.41; 95% CI, 0.32-0.52; \( P < .0001 \)).\(^2\) The median overall survival with sacituzumab govitecan was 12.1 months (range, 10.7-14.0) vs 6.7 months (5.8-7.7) with physician’s choice (HR, 0.48; 95% CI, 0.38-0.59; \( P < .0001 \)).

**CARR:** The data look great, of course [From the Data].\(^2\) Median overall survival doubled, and PFS [tripled].\(^1,2\) When you see a PFS of about 6 months, it’s not impressive to most physicians; but in this case, it is. That gets you through maybe 2 scans, where you can give a patient some good news and a bit of benefit where they may have not had that result with the previous scans. So it gives them something to celebrate in this situation. Overall it looks good. I think everybody would agree with that, compared with the physician’s choice or other chemotherapies we use in this space.

**HAMILTON:** Yes, I think you bring up a good point. That information helps you with what line you are using regimens and whether there is a certain time that you need to use something else. Certainly, that’s the case for PD-L1 testing; we’ve got to [test] that right out of the gate. We’ve got to do it first line, or we lose the opportunity.

**GHANEM:** Yes, I don’t start anyone before I do BRCA1, BRCA2, and PD-L1 [testing] at least. It helps you even with choosing the chemotherapy. If the patient is BRCA positive, you would lean toward a carboplatin regimen, and [also] if the patient is PD-L1. So I don’t start treatment before I do the molecular and genetic testing.

**WILLIS:** I also always try to make sure I do the molecular panels and the genetic testing as early as I can, so I can direct them toward a particular clinical trial or give them the most appropriate agent. In those molecular panels, one of the new targets—and I know that with the sacituzumab, they are looking at Trop-2 as a possible target, especially—I think it’s more than 80% of patients with TNBC also have Trop-2, so I don’t know how that correlates with the response rate, but I think it’s something that I would look at in terms of moving it to second line vs third line.

**HAMILTON:** Yes, you’re right. We don’t have any data right now about needing to use Trop-2 to pick who is or is not eligible or who might respond to sacituzumab. So what are you going to use most often as the next therapy after sacituzumab? Are you picking that based on ease of administration, based on what AEs the patient may have, and what you think they might tolerate best?

**HEMPHILL:** At that point, this is all palliative. It’s the AE profile. [I might choose] capecitabine, potentially, just to keep them out of the clinic, so they can enjoy their families as much as they can, because we know it’s inevitably going to [progress eventually].

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**FROM THE DATA**

**FROM THE DATA**

[From the Data]
But for sacituzumab, is there any clinical benefit whatsoever in the low ER/PR [estrogen receptor/progesterone receptor] level, like the old WHO [World Health Organization] definition, less than 10%? Would you still think about it, given the significant improvement for the patients with TNBC?

HAMILTON: I definitely would. Those patients were not included in the clinical trial. We enrolled another clinical trial for the ER-positive patients. [According to data presented at the 2022 American Society of Clinical Oncology Annual Meeting,] sacituzumab did beat standard chemotherapy in the third-line setting for hormone receptor–positive patients. I anticipate an approval for ER-positive patients by the end of the year.

I think that brings up a good point between clinical trials and real-world settings. Clinical trials often require an ER of 0, but what about our patient who has an ER expression of 10%? You’re not going to rely on endocrine therapy in that patient, yet they’re not strictly triple negative. And many patients, unfortunately, fall into that gray window. But yes, I think very soon you will be able to use sacituzumab for patients with HER2-negative disease, triple negative, or hormone receptor positive. That was a good question.

HAMILTON: If you aren’t using sacituzumab in the second line, what are you using, and why? Are you thinking, “It’s a new drug, and I just don’t feel as comfortable with it for my patients yet”? Is there something about it you don’t like? Or had you not yet heard the good news that you could be using it in the second line?

ZAYDAN: I’m reserving it as third or fourth line after I try my other options. I am concerned about the AEs. And psychologically, if I use sacituzumab, and it fails, what do I do next?

WILLIS: I’m thinking that second line makes the most sense, in terms of using your best drug that you have. Because when you look at quality of life—honestly, when I see folks getting other regimens, you see that the response rate isn’t that good, and also, every time you give a regimen, it’s just that quality of life is going to take a hit every time.

The AE profile is good. Honestly, I have a hard time giving eribulin, in terms of the neutropenia, in terms of the frequency of dosing. So I don’t see that much difference because you give it on the same [schedule] as you do the sacituzumab.

HAMILTON: Yes, on days 1 and 8?

WILLIS: Yes, so I think it’s a very good agent. One of the big issues that some physicians may have is that initially everybody thought it was going to be approved, and suddenly it got niched and pretty much put off for about a year. I think that’s what makes some people uncomfortable.

But I couldn’t wait for it to come out. I was disappointed when it didn’t come out initially. I like the agent, and I honestly think it should be second line, in terms of that healthy patient or that young patient who’s out there. Some of the patients I’ve treated with it, we talk about that 1 year [median OS]; I’ve not seen that with any other agent. I’m always having to change the agent. So I’d want to give them the best agent up front, especially if the toxicity profile is pretty good.

DISCUSSION QUESTION

Which efficacy end points are most meaningful for you?

HEMPHILL: I agree with Dr Willis. From the efficacy and pretty minimal toxicity standpoint, I think it should be definitely [used in the] second line.

HAMILTON: Do you care about the survival, the PFS, the response rate, time to response? What do you think is most important for you and your patient?

WILLIS: I am a huge fan of the clinical benefit ratio. I know that at this stage, most patients may not respond. They may have stable disease [SD]. And I like clinical benefit as the best measure when I’m dealing with someone with metastatic disease who I know I may not be able to cure, but I may be able to help them.

HAMILTON: Yes, so you’re looking for [no progressive disease]?

WILLIS: Correct.

GIAN: I concur with that.

ZAYDAN: They are all important. The patient is thinking of survival, but as a physician I think PFS includes everything, practically; like how long it will take for progression, even if their response is SD. I think PFS is the best measure I look at.
Tewari Reviews First-line Maintenance Options in Advanced Ovarian Cancer

CASE

- A 49-year-old woman presented to her primary care physician complaining of abdominal bloating and nausea.
- Medical history of mild hypertension
- Family history: mother died of breast cancer at age 59 years; cousin on mother’s side died of ovarian cancer at age 65 years
- CT scan showed small-volume ascites, bilateral 8-cm adnexal masses
- Cancer antigen 125: 285 U/mL
- She underwent exploratory laparotomy followed by omentectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, appendectomy, and resection of pelvic nodules for stage IIIC high-grade serous ovarian cancer.
- Gross residual disease (1.1 cm) after surgery

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Targeted Oncology™: What are the key studies of first-line maintenance therapy after platinum-based chemotherapy for ovarian cancer?

TEWARI: We have had quite a few randomized phase 3 clinical trials of therapy in this setting: GOG-0218 [NCT00262847], SOLO-1 [NCT01844986], PRIMA [NCT02655016], and PAOLA-1 [NCT02477644]. The last 3 studies focused on PARP inhibitors, as opposed to GOG-0218, the first [whose results were] published, which focused on bevacizumab [Avastin].

One of the things I want to draw attention to in these trials is the type of tumor testing that the patients underwent. GOG-0218 was an all-comers trial, and only post hoc did we study homologous recombination repair enzymes. In SOLO-1, all the patients had a BRCA mutation, [either] germline or somatic. In the PRIMA trial, which focused on niraparib [Zejula], patients were invited to participate regardless of their mutation status, though there was an analysis of the homologous recombination deficiency [HRD]–positive patients. PAOLA-1, which studied bevacizumab plus olaparib [Lynparza], also invited all comers, but a lot of the focus was on the BRCA-mutated population. All these clinical trials are remarkable for having met their progression-free survival [PFS] end point, which was the primary end point in each of these studies.

What are the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of patients with a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer?

The standard of care up front is cytoreductive surgery, followed by 6 cycles of platinum- and taxane-based chemotherapy. We do know that depending on the patient’s tumor distribution and medical comorbidities, sometimes neoadjuvant chemotherapy is administered, followed by interval surgical cytoreduction and then additional adjuvant chemotherapy. For patients who have stage II to IV advanced epithelial ovarian, tubal, or peritoneal cancer, and who have completed chemotherapy, [the choice of maintenance therapy depends on] whether the patient received bevacizumab as part of primary therapy or not.¹

According to the NCCN guidelines, if they did not receive bevacizumab as part of primary therapy, the patient should undergo germline and somatic testing. If their BRCA 1/2 status is wild type or unknown, [and] if they had a complete response [CR] or partial response [PR] to systemic therapy, options for maintenance therapy are either observation or the PARP inhibitor niraparib, which is given once daily. Alternatively, if the patient had stable disease or progression, they should be treated appropriately according to available rescue remedies or go on to a clinical trial.¹

If patients did not receive bevacizumab, and they are found to have a germline or somatic BRCA1 or BRCA2 mutation, [and] if they had a CR or a PR, options in those cases are either olaparib as a mono-maintenance therapy

continued on page 52
A BALANCED APPROACH TO TREATMENT

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC Patients

INDICATIONS
CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using anti-diarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 8% patients, of whom 12% (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=35) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%) and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (1/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=43) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks.
ONJ (cont’d): prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients. Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN. In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients. Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (~20%) adverse reactions are: CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

ONJ = osteonecrosis of the jaw.

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION. PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION. INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differentiated Thyroid Cancer
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with loco-regional or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or intolerant.

2 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in the RCC, HCC, and DTC studies.

5.2 Perforations and Fistulas
Fistulas were rare, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in 0.2% of CABOMETYX-treated patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was the most common adverse reaction in CABOMETYX-treated patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment and discontinue CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, discontinue CABOMETYX and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST ≥ 3 times ULN (Grade ≥2) was reported in 83 patients of whom 23 (28%) received systemic corticosteroids: ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=35), one patient with a single administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral and malformational mists in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypercalcemia, Hypothyroidism, Hyperparathyroidism, Hypothyroidism, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), in 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), and in combination with nivolumab 240 mg/m2 every 2 weeks in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER). 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.

Renal Cell Carcinoma

MELANOMA

Therapy of choice is surgical resection or inoperable stages of disease. Once metastatic disease or recurrence is documented, CABOMETYX is indicated for the treatment of patients with metastatic or unresectable, chemotherapy-naive, metastatic melanoma with progression on or after a prior anti-CTLA-4 agent. CABOMETYX is indicated for the treatment of patients with metastatic melanoma with progression on or after a prior anti-PD-1/PD-L1 agent. CABOMETYX is indicated for the treatment of patients with metastatic melanoma with progression on or after a prior anti-CTLA-4 and anti-PD-1/PD-L1 agent. CABOMETYX is indicated for the treatment of patients with metastatic melanoma patients with progression on or after a prior anti-CTLA-4, anti-PD-1/PD-L1, and tyrosine kinase inhibitor.
### CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib. Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypoglycemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypertension, and syncope.

### CHEKOMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHEKOMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

### Table 3. Grade 3-4 Adverse Reactions Occurring in ≥1% of Patients Who Received CABOMETYX in CABOSUN

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Patients with Grade 3-4 Adverse Reaction</th>
<th>Percentage (%) of Patients</th>
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</thead>
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<tr>
<td>Gastrointestinal</td>
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</tr>
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<tr>
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<td>3.7</td>
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<tr>
<td>Vomiting</td>
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<td>1.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>1.3</td>
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<tr>
<td>General</td>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Pain</td>
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<td></td>
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<td>Metabolism and Nutrition</td>
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<tr>
<td>Hyperkalemia</td>
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<td>3.7</td>
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<tr>
<td>Hypomagnesemia</td>
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<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
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<td></td>
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<tr>
<td>Palmoplantar erythrodysesthesia</td>
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<td>Skin ulcer</td>
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<td>29.1</td>
</tr>
<tr>
<td>Angiopathy</td>
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<td>1.3</td>
</tr>
<tr>
<td>Investigations</td>
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<td></td>
</tr>
<tr>
<td>Increased ALT</td>
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<td>5.9</td>
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<tr>
<td>Weight decreased</td>
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<tr>
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<td>3.7</td>
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<td>Thrombocytopenia</td>
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<td>1.3</td>
</tr>
<tr>
<td>Nervous System</td>
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<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>5</td>
<td>5.9</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
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<tr>
<td>Dyspnea</td>
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<td>1.3</td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
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<td></td>
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<td>Anemia</td>
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<td>1.3</td>
</tr>
<tr>
<td>Psychiatric</td>
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<td></td>
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<tr>
<td>Depression</td>
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<td>4.8</td>
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<tr>
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<tr>
<td>Infections</td>
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<tr>
<td>Lung infection</td>
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<td>4.8</td>
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<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<td></td>
</tr>
<tr>
<td>Back pain</td>
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</tr>
<tr>
<td>Bone pain</td>
<td>3</td>
<td>3.7</td>
</tr>
<tr>
<td>Pain in extremity</td>
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<tr>
<td>Arthralgia</td>
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### Table 4. Adverse Reactions in ≥1% of Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Percentage (%) of Patients</th>
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<tr>
<td>Gastrointestinal</td>
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<td>Diarrhea</td>
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<tr>
<td>Vomiting</td>
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<td>Constipation</td>
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<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
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<tr>
<td>Increased ALT</td>
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<tr>
<td>Weight decreased</td>
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<td>Increased AST</td>
<td>3</td>
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<tr>
<td>Increased blood pressure</td>
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<tr>
<td>Lymphopenia</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Nervous System</td>
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</tr>
<tr>
<td>Syncope</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
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<td>Dyspnea</td>
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<td>Blood and Lymphatic</td>
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<td>Infections</td>
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<td>Musculoskeletal and Connective Tissue</td>
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<td>Pain in extremity</td>
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### Table 2. Laboratory Abnormalities Occurring in ≥25% of Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=331)(^1)</th>
<th>Everolimus (n=322)(^1)</th>
<th>Percentage (%) of Patients</th>
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<tbody>
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<td>Chemistry</td>
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<tr>
<td>Increased ALP</td>
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<tr>
<td>Increased creatinine</td>
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<td>71</td>
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<tr>
<td>Increased uric acid</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>27</td>
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</tr>
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| ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase. \(^1\) Based on laboratory abnormalities.
Adverse Reactions

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX</th>
<th>Nivolumab (n=320)</th>
<th>Suninitib (n=230)</th>
<th>Percentage (%) of Patients</th>
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<tr>
<td>Chemistry</td>
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<td>0.8</td>
<td>14</td>
<td>0.4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>42</td>
<td>6.6</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>41</td>
<td>0.3</td>
<td>70</td>
<td>9.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>37</td>
<td>2.5</td>
<td>61</td>
<td>21.5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>37</td>
<td>0.3</td>
<td>66</td>
<td>2.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35</td>
<td>3.2</td>
<td>67</td>
<td>12</td>
</tr>
</tbody>
</table>

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: CABOMETYX and nivolumab-checkmate-eight. (n=170 to 317 patients) and suninitib group (range: 173 to 311 patients).


differentiated Thyroid Cancer

The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced, differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.3 – 11.6) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 55% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPE, fatigue, hyperpigmentation, and stomatitis. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in 22% included diarrhea, pleural effusion, pulmonary embolism, and dyspnea. Fatal adverse reactions occurred in 16% of patients in the CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%).

The median average daily dose was 42.0 mg for CABOMETYX. The dose was reduced in 56% of patients receiving CABOMETYX: 22% of patients required a second dose reduction. The most frequent adverse reactions leading to dose discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. Adverse reactions leading to permanent discontinuation of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were: PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

**Table 6. Adverse Reactions Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n = 467)</th>
<th>Placebo (n = 237)</th>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>&lt;1</td>
<td>12</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>10</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Asthma</td>
<td>22</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>48</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodyssthesia</td>
<td>46</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>21</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>30</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Investigations</td>
<td>17</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX</th>
<th>Placebo (n=237)</th>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LDH</td>
<td>89</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>74</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>Increased AST</td>
<td>73</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>51</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>43</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>25</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>22</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>16</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>54</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>43</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Increased hemoglobin</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4).
2 Includes the following terms: hypertension, blood pressure increased, blood pressure systolic increased.
3 Includes gastroesophageal reflux disease.
4 Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4).
5 Includes alcohol, tobacco consumption.
6 Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4).
7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

Co-administration of a strong CYP3A4 inhibitor with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid co-administration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if co-administration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure to cabozantinib.

Strong CYP3A4 Inducers

Co-administration of a strong CYP3A4 inducer capsule formulation with a strong CYP3A4 inducer increases the exposure of cabozantinib, which may reduce efficacy. Avoid co-administration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if co-administration with strong CYP3A4 inducers cannot be avoided. Avoid St. John’s wort which may also decrease exposure of cabozantinib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women administered orally or intravenously. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rabbits and rats during organogenesis resulted in embryo/foetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended 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 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a peri- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation
Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females
Advises females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility
Females and Males

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients randomized to CABOMETYX administered with rilpultumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolism have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for prompt treatment of symptoms or signs of palmoplantar rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hyponatremia: Advise patients that CABOMETYX can cause low serum levels and that their serum sodium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Embryo-fetal toxicity:

• Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

• Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John’s wort.

Important administration information

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information.

Revision 10/2021

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Continued from page 45

or niraparib as a mono-maintenance therapy. Both of those are considered to be category 1 regimens; olaparib, by virtue of the SOLO-1 study, and niraparib, by virtue of the PRIMA study. Importantly, the olaparib indication requires the patient to have a germline or a somatic BRCA mutation, whereas niraparib [is indicated] regardless of mutational status, or what we refer to as a molecular signature.

If bevacizumab was given with chemotherapy, the options are as follows: patients who have a CR and a BRCA1/2 status of wild type or unknown can continue with bevacizumab as a maintenance monotherapy; you can use bevacizumab plus olaparib if, upon tumor testing, a patient is found to be HRD positive. If, however, a patient is found to have a germline or somatic BRCA1/2 mutation and has experienced a CR or PR, there are 3 options: the category 1 combination of bevacizumab plus olaparib, as per PAOLA-1; olaparib as per SOLO-1; or niraparib as per PRIMA. One of the things that should stand out is that niraparib is available to be used in many clinical situations, regardless of molecular signature. Its use doesn’t depend on having a BRCA mutation [and] doesn’t depend on having HRD in the tumor, whereas olaparib requires a germline or somatic mutation, and the combination of bevacizumab plus olaparib requires HRD in the tumor.

What key data from SOLO-1 support the use of olaparib as a single-agent maintenance therapy after first-line chemotherapy?

This study was a randomized phase 3 trial, in which all the patients had to have a germline or somatic BRCA1/2 mutation. Nearly 400 patients were randomly assigned 2:1 to receive either olaparib 300 mg twice daily or placebo, respectively. The primary end point was investigator-assessed PFS.

By the 5-year follow-up, a remarkable [difference in PFS had been] maintained. Median PFS in the experimental and control groups was [56.0] months vs 13.8 months, respectively [HR, 0.33; 95% CI, 0.25-0.43]. Remember, this is a select group of patients [comprising] a favorable prognostic group, [with each patient having] a BRCA1 or BRCA2 mutation. Certainly, we need to talk about [the known adverse event (AE) of] myelodysplastic syndrome [MDS] and the risk of acute myeloid leukemia; for patients getting any of the PARP inhibitors, the risk is about 1% to 2%. It’s not yet clear whether this effect is caused by the PARP inhibitor or by the prior chemotherapy. Still, the PFS data [from SOLO-1 are] just amazing.

The subgroup analysis of PFS revealed that the PARP inhibitor did benefit many subpopulations, [including those defined by] age, stage at diagnosis, and the presence of residual macroscopic disease. Remember, [these subgroup analyses] are not powered to study each of these separate factors, but are hypothesis generating and can guide subsequent clinical trial design.

At 5 years of follow-up, the safety profile [of the initial report] was sustained. There were no additional cases of MDS, and the incidence of new primary malignancies was balanced between arms.

How does PRIMA support the use of niraparib as maintenance therapy in high-risk patients of any BRCA status with first-line ovarian cancer?

The PRIMA trial, like SOLO-1, was a randomized phase 3 trial. These patients had received frontline systemic chemotherapy and were randomly assigned 2:1 to receive either niraparib at 300 mg daily or placebo, respectively. The primary end point was PFS, which was determined by a blinded independent radiology committee. This study enrolled a high-risk population, which included patients with wild-type BRCA. Many of these patients had advanced disease [36.2% having stage IV], and a significant percentage of the patients [had] received neoadjuvant chemotherapy [66.7%]. When you review the results of PRIMA, it’s remarkable how well the PARP inhibitor worked, even in this high-risk setting. In my opinion, the population of the PRIMA study [vs that of SOLO-1 better represented the] real-world population, because it took all comers. Patients weren’t weeded out by BRCA status.

In the intention-to-treat population, median PFS for the experimental and control groups was 13.8 months vs [8.2] months, respectively [HR, 0.62; 95% CI, 0.50-0.76; P < .001]. In the HRD-positive population, the median PFS jumps to [21.9] months vs [10.4] months, respectively [HR, 0.43; 95% CI, 0.31-0.59; P < .001]. These are remarkable [data], equally as compelling as the SOLO-1 [data, which are some] of the most cited survival [data] in this disease.

Even among the HRD-positive [patients with] wild-type BRCA, there was a separation [of the median PFS values] for the experimental and control groups [19.6 months vs 8.2 months, respectively; HR, 0.50; 95% CI, 0.31-0.83]. In the HRD-positive, BRCA-mutated group, the median PFS was [22.1 months vs 10.9 months, respectively; HR, 0.40; 95% CI, 0.27-0.62]. Now, 22 months is not [as high as] 56 months, which we saw in the 5-year follow-up of SOLO-1, but remember these 2 things: number 1, these BRCA-mutated patients were a higher-risk group, and number 2, we don’t have 5 years of follow-up yet for this population.

Subgroup analysis revealed that niraparib worked better for [subgroups defined by most parameters], although for patients with stage IV disease and those with undetermined HRD status, [the data do not show a conclusive benefit].
The prespecified interim analysis of the key secondary end point is also remarkable. At a follow-up of 2 years, overall survival in the overall population [was 84% in the experimental group vs 77% in the control group]. However, because the number of deaths was relatively low, we cannot draw definitive conclusions at this time. But in the HRD-positive population, the HR for death was 0.61 [95% CI, 0.27-1.39]; in the intention-to-treat population, the HR was [0.70; 95% CI, 0.44-1.11]. Even in the HRD-negative, or homologous repair–proficient, population, the HR was 0.51 [95% CI, 0.27-0.97]; the survival rate at 2 years was 81% among patients who received niraparib and 59% among patients who received placebo. So we can’t draw definitive conclusions from this, because the [number of] events was low, but numerically, these are compelling data.

[Among the observed AEs], thrombocytopenia was [prominent], with 29% of patients receiving niraparib experiencing grade 3 or higher [Figure 7]. In this trial, the starting dose was 300 mg, and that was based on the approved dose as determined by the NOVA trial [NCT01847274] for patients with platinum-sensitive recurrent disease and by the QUADRA trial [NCT02354586] for HRD-positive patients in need of therapy for the fourth line and beyond. But when PRIMA led to FDA approval, the FDA saw that the majority of patients underwent a dose reduction, and so the dose was changed to 200 mg.

What data support the use of bevacizumab plus olaparib for first-line maintenance after bevacizumab plus platinum chemotherapy?

The PAOLA-1 study [investigated the use of this maintenance combination]. Patients received olaparib 300 mg twice daily with either bevacizumab 15 mg/kg every 3 weeks or placebo. The patients in PAOLA-1 were an all-comers population. The primary end point was PFS. There was a [clear difference in PFS] between the experimental and control groups, with an HR of 0.59 [95% CI, 0.49-0.72; P<.001]. This led to FDA approval of this combination, but only in the HRD-positive population.

![Figure 7. Rate of Adverse Events With Niraparib in the PRIMA Trial](image-url)
When subgroup analysis was performed on groups defined by HRD status, there was a [definite benefit from olaparib vs placebo] in the HRD-positive cohort [when patients with mutated BRCA were included]; median PFS was 37.2 months vs 17.7 months, respectively [HR, 0.33; 95% CI, 0.25-0.45].

When patients with a BRCA mutation were eliminated from the HRD-positive cohort, the median PFS decreased a bit [to 28.1 months vs 16.6 months, respectively (HR, 0.43; 95% CI, 0.28-0.66)]. [In the cohort of] HRD-negative patients, the median PFS was [16.9 months vs 16.0 months (HR, 0.92; 95% CI, 0.72-1.17)]. This is a different result than that which we saw with PRIMA, in which HRD-negative patients showed a benefit.

This is why the combination of bevacizumab plus olaparib did not get approval in the HRD-negative population like niraparib did.  

Why do you think niraparib had a benefit in the HRD-negative population and olaparib did not, given that both are PARP inhibitors?

We’re not sure. The PARP inhibitors were designed for patients whose tumors were HRD positive, by virtue of a BRCA mutation or a mutation in something else, such as RAD51C, RAD51D, or BRP1. So I agree that it is astonishing to see activity in the HRD-negative population. Some people have speculated that niraparib has another mechanism of action, separate from its PARP inhibition. We don’t know. We know that bevacizumab is active [in HRD-negative patients], and one would think that the combination of bevacizumab plus olaparib would [perform even better], but it did not.

I do know that in all 3 trials, [adherence to protocol] was pretty good. However, we have to remember most of the patients in PRIMA did have a dose reduction, because it was difficult [for them] to tolerate 300 mg daily.

What did subgroup and safety analyses reveal in the PAOLA-1 trial?

Subgroup analysis showed that if the tumor status were HRD negative or unknown, the [regimen conferred little to no benefit], but if the tumor were HRD positive, [there was a definite benefit (HR, 0.33; 95% CI, 0.25-0.45)]. AEs were important to record, because this trial combined 2 therapies. Bevacizumab has known risks for hypertension, proteinuria, bleeding, thromboembolic phenomenon, and sometimes gastrointestinal perforation, although [that is now less of a concern]. To this was added a PARP inhibitor. However, no major safety signals were identified in the PAOLA-1 trial, which suggests that you can combine these medicines safely.

The most common AEs in the SOLO-1, PRIMA, and PAOLA-1 trials, [considered together], included hypertension. Of course, that was because of the bevacizumab from PAOLA-1. But overall, thrombocytopenia turned out to be the [biggest concern], especially in the PRIMA trial of niraparib, in which 39% of patients experienced thrombocytopenia of grade 3 or 4.

How have the indications and dosing recommendations for niraparib evolved since its initial approval?

Niraparib was first approved for use in platinum-sensitive recurrent ovarian cancer, on the basis of the NOVA study, at a dosage of 300 mg daily. Then the QUADRA study was done in the HRD-positive population, assessing the use of niraparib for fourth-line therapy and beyond. It [became] evident that thrombocytopenia was a major problem [when the drug was used at a] 300-mg starting dose, [but]...an analysis suggested that if a patient’s body weight was [not more than] 77 kg, or their platelet count [was not more than] 150,000/μL, 200 mg would be a more appropriate starting dose. We adopted that in clinical practice without [any recommendation from the] FDA. It was important to study this individualized niraparib dosing prospectively, in the primary maintenance setting.

What dose adjustments are recommended for olaparib and niraparib?

For olaparib, the starting dose is 300 mg twice a day, [in the form of] two 150-mg tablets in the morning and 2 tablets in the evening. Originally, olaparib was in capsule form, and patients had to take [many more] capsules in the morning and in the evening, which resulted in a lot of abdominal discomfort. Now we have the tablets. The first dose reduction brings the dose down to 250 mg twice a day; the second reduction brings the dose to 200 mg twice a day. With niraparib, the starting dose depends on the [patient’s weight and platelet count]. If you start at 300 mg, the subsequent reductions progress to 200 mg and then to 100 mg. If you start at 200 mg, you can reduce the dose to 100 mg, and [after that you would] discontinue.

How do the results of the PRIME (NCT03709316) study of niraparib inform the choice of starting dose?

In this study, the individualized starting dose was prospectively evaluated in a randomized clinical trial, and the median PFS was 24.8 months [95% CI, 19.2-not evaluable] for the niraparib group and 8.3 months [95% CI, 7.3-11.1] for the control group. Analysis of cohorts defined by HRD status and BRCA status showed that the median PFS was not reached in the HRD-positive cohort or in the cohort with germline BRCA mutations. In the cohort with nongermline BRCA mutations, the median PFS in the experimental and control groups was 19.3 months and 8.3 months, respectively [HR, 0.48; P < .001].
AEs led to discontinuation in 6.7% of the experimental group; this is the lowest rate in any clinical trial studying a PARP inhibitor. And so, the RADAR [Research on Adverse Drug Events and Reports] analysis, which was a retrospective, ad hoc, hypothesis-generating analysis that we put into practice for platinum-sensitive recurrent ovarian [cancer], was prospectively validated in the primary-maintenance setting. ■

REFERENCES
Roundtable Discussion: Manasanch Explores BMCA-Targeted Management of Relapsed/Refractory Multiple Myeloma

CASE SUMMARY

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 an autologous stem cell transplant. The patient achieved a very good partial response. He received lenalidomide maintenance and planned to continue it until progression. After 3 years, the patient progressed and was treated with daratumumab (Darzalex), pomalidomide (Pomalyst), and dexamethasone.

One year later, a PET scan showed new lytic lesions associated with hypermetabolic activity. He had an ECOG performance status of 2. Repeat bone marrow biopsy showed del(17p) in 50% of cells, hyperdiploid.

Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.5 g/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.8 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1 mg/dL</td>
</tr>
<tr>
<td>M spike</td>
<td>1.4 g/dL</td>
</tr>
<tr>
<td>Light chain levels</td>
<td>Rising</td>
</tr>
</tbody>
</table>

POLLING QUESTION

“What are you most likely to recommend for this patient outside a clinical trial?”

- Belantamab mafodotin 55% (6)
- Carfilzomib plus selinexor plus dexamethasone 36% (4)
- Alsatuximab plus carfilzomib plus dexamethasone 9% (1)
- Other 0% (0)

Total votes: 11

DISCUSSION QUESTIONS

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

continued on page 66
See a spectrum of results

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

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

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

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

Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials. Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%). Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who 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 ≥ 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.

• 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
**SELECTED SAFETY INFORMATION**

**Warnings and Precautions (cont’d)**

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

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

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

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

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

Visit [www.LENVIMA.com/hcp](http://www.LENVIMA.com/hcp) to learn more.
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 was observed post baseline in 70% of LENVIMA–treated patients in RCC and 60% of LENVIMA + everolimus–treated patients in RCC.

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

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

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

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

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

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

Adverse Reactions

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus–treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (8%), thrombotic thrombocytopenia (8%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 85% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombotic thrombocytopenia (6%), vomiting (6%), nausea (6%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 25% of patients.

Use in Specific Populations

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

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

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

Please see Brief Summary on the following pages.

LENNIMA® (raretron) capsules BRIEF SUMMARY – See package insert for full prescribing information.

INDICATIONS AND USAGE
LENNIMA is a kinase inhibitor that is indicated:
- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
- In combination with pembrolizumab, for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

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: 10 mg orally once daily.

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

**Differentiated Thyroid Cancer (DTC)**
- **Single Agent Therapy:**
  - 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.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modifications for LENVIMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Grade 3</td>
<td>Withhold for Grade 3 that persists despite optimal antihypertensive therapy.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Cardiac Dysfunction</td>
<td>Grade 3</td>
<td>Withhold until improves to Grade 0 or 1. Baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Arterial Thromboembolic Event</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Renal Failure or Impairment</td>
<td>Grade 3</td>
<td>Withhold until improves to Grade 0 or 1. Baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 g or greater proteinuria in 24 hours</td>
<td>Withhold until less than or equal to 2 g of protein per 24 hours.</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Withhold until improves to less than or equal to 48 g of protein per 24 hours.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>Any Grade</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Fistula Formation</td>
<td>Grade 3</td>
<td>Withhold until improves to Grade 0 or 1. Baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Greater than 500 ms or greater than 60 ms increase from baseline</td>
<td>Withhold until improves to less than or equal to 480 ms or baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Withhold until improves to less than or equal to 480 ms or baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Reversible Posterior Leukoencephalopathy Syndrome</td>
<td>Any Grade</td>
<td>Withhold until fully resolved.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Persistent or intolerable</td>
<td>Withhold until improves to Grade 0 or 1. Baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
</tbody>
</table>

**Diarrhea**
- 0.4 mg yellowish-red body and yellow-red cap, marked in black ink with “EC” on cap and “LENNIM 4 mg” on body.

**Contraindications**
- None.

**Warnings and Precautions**

**Hypertension**
- Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 19 days in SELECT and 29 days in REFLECT (HCC).
- Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred <1% in SELECT and Grade 4 hypertension was not reported in REFLECT.
- In patients receiving LENVIMA 18 mg orally once daily with everolimus in study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 25 days.
- Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure >180 mm Hg occurred in 29% of patients and diastolic blood pressure ≥100 mm Hg occurred in 21%.

**Serious complications of poorly controlled hypertension have been reported.**

**Control blood pressure prior to initiating LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity.**

**Cardiac Dysfunction**
- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 789 patients with DTC or RCC, 3% had cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, conduction defects, heart failure, cardiac failure, cardiac failure, cardiac failure), occurred in 5% of patients. During long term administration, the median time to onset of new or worsening cardiovascular events was 24 days in SELECT and 32 days in REFLECT (HCC).
- In patients with advanced RCC treated with LENVIMA, 1% of patients had a cardiac event within the previous 6 months.

**Diarrhea**
- Diarrhea was the most frequent cause of dose interruption/reduction and diarrhea recurred in 19% of patients.
- Diarrhea was the most frequent cause of dose interruption/reduction and diarrhea recurred in 19% of patients.

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

**Renal Cell Carcinoma (RCC)**
- In combination with pembrolizumab, for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

**Recommended Dosage Modifications for Adverse Reactions for LENVIMA in Combination with Pembrolizumab**
- When administering LENVIMA in combination with pembrolizumab, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA as shown in Table 1. Refer to pembrolizumab prescribing information for additional information about dosage modification.

**Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Everolimus**
- When administering LENVIMA in combination with everolimus, withhold or reduce the LENVIMA dose first and then the everolimus dose for adverse reactions of both LENVIMA and everolimus. Refer to the everolimus prescribing information for additional dosage modification information.

**Dosage Modifications for Severe Renal Impairment**
- The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma and severe renal impairment (creatinine clearance <30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is:

<table>
<thead>
<tr>
<th>Indication</th>
<th>First Doseage Reduction To</th>
<th>Second Doseage Reduction To</th>
<th>Third Doseage Reduction To</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTC</td>
<td>4 mg orally once daily</td>
<td>2 mg orally once daily</td>
<td>Discontinue</td>
</tr>
<tr>
<td>RCC</td>
<td>4 mg orally once daily</td>
<td>2 mg orally once daily</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Endometrial Carcinoma</td>
<td>4 mg orally once daily</td>
<td>2 mg orally once daily</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**Dosage Modifications for Severe Hepatic Impairment**
- The recommended dosage of LENVIMA for patients with advanced RCC, EC, and endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is:

<table>
<thead>
<tr>
<th>Indication</th>
<th>First Doseage Reduction To</th>
<th>Second Doseage Reduction To</th>
<th>Third Doseage Reduction To</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>4 mg orally once daily</td>
<td>2 mg orally once daily</td>
<td>Discontinue</td>
</tr>
<tr>
<td>RCC</td>
<td>2 mg orally once daily</td>
<td>1 mg orally once daily</td>
<td>Discontinue</td>
</tr>
<tr>
<td>RCC</td>
<td>1 mg orally once daily</td>
<td>1 mg orally once daily</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**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%.

**Diabetes**
- In Study 206 (RCC), diabetes occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 in 19%. Diabetes was the most frequent cause of dose interruption/reduction and diabetes recurred despite dose reduction.
The safety of LENVIMA was evaluated in SELECT, in which patients with radioactive iodine-refractory Differentiated Thyroid Cancer (DTC) were treated with LENVIMA with or without everolimus. In SELECT, Grade 3 or 4 fistula occurred in 11% of patients receiving LENVIMA with everolimus and QTc interval increases of >60 ms occurred in 2% of patients receiving LENVIMA with or without everolimus. QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA with everolimus and QTc interval increases of >100 ms occurred in 2% of patients receiving LENVIMA with everolimus. In REFLECT (HCC), QTc interval increases of >60 ms occurred in 8% of patients receiving LENVIMA with everolimus and QTc interval increases of >500 ms occurred in 3% of patients receiving LENVIMA with everolimus. QTc interval increases of >500 ms occurred in 6% of placebo recipients in the double-blind phase of the study.

The most common adverse reactions observed in LENVIMA-treated patients (≥30%) were: nausea, vomiting, anorexia, hypothyroidism, hypertension, fatigue, loose stools, weight loss, and pyrexia. The most common adverse reactions (≥2%) were: peripheral edema, hypertension (13%), dyspnea (11%), nausea (10%), and constipation (10%). The most common adverse reactions (≥1%) occurring in ≥10% of patients treated with LENVIMA and placebo were: diarrhea (13% vs 3%), hypertension (11% vs 4%), and arthralgia (8% vs 5%).

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

The following laboratory abnormalities (all Grades) occurred in ≥15% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypocalcemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum albumin, and hyperlipidemia.

The data below reflect exposure to LENVIMA in 1557 patients enrolled in randomized, active-controlled trials across the clinical development program. Some of the adverse reactions reported in clinical trials occurred at rates that may not be directly comparable to those observed in routine clinical practice, and, while included in this labeling, may not reflect the experience of patients treated in routine clinical practice. These include:

- QT Interval Prolongation
- Hemorrhagic Events
- Nausea
- Hypothyroidism
- Hypertension
- Vomiting
- Abdominal pain
- Constipation
- Oral pain
- Dry mouth
- Pruritus
- Gastrointestinal Perforation
- Thrombocytopenia
- Metabolism and Nutrition
- Arthralgia/myalgia
- Respiratory, Thoracic and Mediastinal
- Fatigue
- Rash
- Dizziness
- Neutropenia
- Hypokalemia
- Palmar-plantar erythrodysesthesia
- Stomatitis
- Oral pain
- Infection
- Urinary tract infection
- Gastrointestinal Perforation
- Thrombocytopenia
- Skin and Subcutaneous Tissue
- Mucosal inflammation
The safety of LENVIMA was evaluated in Study 205, in which patients with unresectable advanced or metastatic RCC were randomized (1:1) to LENVIMA with everolimus (n=11). The median treatment duration was 8.1 months for LENVIMA with everolimus. Among 62 patients who received LENVIMA with everolimus, the median age was 61 years, 71% were men, and 98% were White.

The most common adverse reactions observed in the LENVIMA with everolimus-treated group (≥30%) were, in order of decreasing frequency, diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, pain in extremity, and pain in jaw.

Adverse reactions leading to dose reductions or interruption in 85% of patients receiving LENVIMA with everolimus. The most common adverse reactions (≥5%) resulting in dose reductions in the LENVIMA with everolimus-treated group were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-planter erythrodysesthesia syndrome (11%), nausea (9%), stomatitis/mucosal ulceration (8%), rash (8%), increased lipase (7%), and increased ALT (5%), and increased increased (2%), dyspnea (2%), and pneumonia (2%).

Chemistry

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>80 19</td>
<td>15 0</td>
<td>76 18</td>
<td>10 0</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>64 5</td>
<td>43 2</td>
<td>45 4</td>
<td>37 2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>61 34</td>
<td>28 2</td>
<td>34 16</td>
<td>29 2</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>59 17</td>
<td>41 1</td>
<td>24 2</td>
<td>10 0</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>58 7 55 2</td>
<td>57 3 50 3</td>
<td>59 7 44 2</td>
<td>54 1 42 1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>55 7</td>
<td>48 2</td>
<td>50 7</td>
<td>48 2</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>49 9</td>
<td>36 3</td>
<td>33 3</td>
<td>30 2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>44 4</td>
<td>33 2</td>
<td>29 1</td>
<td>21 1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>42 2</td>
<td>35 1</td>
<td>23 1</td>
<td>20 1</td>
</tr>
<tr>
<td>Increased AST</td>
<td>40 1</td>
<td>25 1</td>
<td>27 1</td>
<td>21 1</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>34 10</td>
<td>22 2</td>
<td>28 10</td>
<td>18 2</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>34 2 30 3</td>
<td>33 3 27 3</td>
<td>34 2 24 3</td>
<td>33 2 23 3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>29 7</td>
<td>70 30</td>
<td>16 8</td>
<td>11 8</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>25 5</td>
<td>15 3</td>
<td>20 4</td>
<td>12 1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>20 1</td>
<td>13 1</td>
<td>15 1</td>
<td>9 1</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>20 2</td>
<td>11 1</td>
<td>15 3</td>
<td>9 3</td>
</tr>
</tbody>
</table>

Table 6: Laboratory Abnormalities in ≥20% of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)

Table 7: Adverse Reactions Occurring in >5% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)
LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 9. REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for Table 9 summarizes the adverse reactions that occurred in ≥10% of patients receiving LENVIMA in REFLECT. Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated erythrodysesthesia syndrome (5%).

The most common adverse reactions with frequency ≥3% were hypertension (4.4%), and urinary tract infection (3.2%). Serious adverse reactions occurred in 50% of these patients receiving LENVIMA and pembrolizumab. Serious fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and pembrolizumab, 7.8 months (range 1.0 to 11.4 months).

In Table 9, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented. In Table 10, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

### Table 7: Adverse Reactions Occurring in >15% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=62</th>
<th>Everolimus 10 mg N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria/Urinary protein present</td>
<td>31 8</td>
<td>14 2</td>
</tr>
<tr>
<td>Renal failure event</td>
<td>18 10</td>
<td>12 2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>37 0</td>
<td>30 0</td>
</tr>
<tr>
<td>Dyspnea/Exertional dyspnea</td>
<td>35 5</td>
<td>28 8</td>
</tr>
<tr>
<td>Anemia</td>
<td>18 0</td>
<td>4 0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 18 mg with Everolimus 5 mg N=62</th>
<th>Everolimus 10 mg N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension/Increased blood pressure</td>
<td>42 13</td>
<td>10 2</td>
</tr>
<tr>
<td>Hemorrhage event</td>
<td>32 6</td>
<td>26 12</td>
</tr>
</tbody>
</table>

+ With at least 1 grade increase from baseline
| Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=278 to 470) and sorafenib group include: epistaxis, hematuria, gingival bleeding, hemoptysis, esophageal stricture, hemorrhagic shock, hypothermia, hemorrhoidal hemorrhage, rectal hemorrhage and upper gastrointestinal hemorrhage.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 8 mg/12 mg N=672</th>
<th>Sorafenib 800 mg N=475</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA (%)</th>
<th>Sorafenib (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased GGT</td>
<td>17 20</td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>15 9</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>7 5</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>3 2</td>
<td></td>
</tr>
</tbody>
</table>
Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common (<5%) adverse reactions resulting in dose reduction of LENVIMA were hypertension (11%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (5%), decreased appetite (6%), asthma (5%), and weight decreased (5%). Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (≥2%) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (8%), decreased appetite (6%), vomiting (5%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2.2%).

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>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>67</td>
<td>0.9</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>3.5</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>25</td>
<td>1.8</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37</td>
<td>2.3</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>35</td>
<td>2.6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>34</td>
<td>2.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>53</td>
<td>2.7</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>7</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>23</td>
<td>2.9</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* Graded per NCI CTCAE v4.03

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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>LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>6</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>60</td>
<td>2.7</td>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>58</td>
<td>9</td>
<td>23</td>
<td>1.6</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>58</td>
<td>9</td>
<td>45</td>
<td>4.4</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>53</td>
<td>6</td>
<td>32</td>
<td>3.8</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>53</td>
<td>9</td>
<td>21</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>33</td>
<td>2.6</td>
<td>23</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypotension</td>
<td>46</td>
<td>15</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43</td>
<td>4.7</td>
<td>18</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* With at least 1 grade increase from baseline

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

<table>
<thead>
<tr>
<th>Endometrial Carcinoma (not MSI-H or dMMR)</th>
<th>LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342</th>
<th>Pembrolizumab N=325</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Test</td>
<td>All Grades* (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Laboratory Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>35</td>
<td>4.7</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>23</td>
<td>2.4</td>
</tr>
<tr>
<td>Increased creatinine lactic</td>
<td>19</td>
<td>3.7</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>18</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Hematology                                  |                 |                |                 |                |
| Lymphopenia                                | 50              | 16             | 65             | 20             |
| Thrombocytopenia                           | 50              | 8              | 36             | 4.7            |
| Aneuploidy                                 | 49              | 8              | 84             | 14             |
| Leukopenia                                 | 43              | 5.5            | 83             | 43             |
| Neutropenia                                | 31              | 6              | 76             | 58             |

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DRUG INTERACTIONS

Drugs That Prolong the QT Interval

LENVIMA may prolong the QT interval. Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval.

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib did not cause adverse pregnancy outcomes at doses up to 24 mg/kg based on body surface area (BSA). However, adverse pregnancy outcomes in rats only occurred at doses ≥30 mg/kg based on BSA. Therefore, LENVIMA should not be administered to pregnant women.

Pediatric Use

LENVIMA is not recommended for use in pediatric patients, including neonates, owing to 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.

---

Carcinogenesis

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

Drug Interactions

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.

---

Contraindication

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

---

Adverse reactions

Adverse reactions due to the mechanism of action of lenvatinib are primarily vascular, including hypertension, edema, and decreased blood pressure.

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Side effects

The most common adverse reactions leading to dose reductions included hypertension, diarrhea, and palmar-plantar erythrodysesthesia syndrome.

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Toxicities

The most common adverse reactions leading to dose reductions included hypertension, diarrhea, and palmar-plantar erythrodysesthesia syndrome.
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 262 patients with renal cell carcinoma (RCC) who received LENVIMA with pembrolizumab in CLEAR, 45% were ≥65 years of age and 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Of the 82 patients with RCC who received LENVIMA with everolimus in Study 208, 36% were ≥65 years of age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between these subjects and younger patients.

Of the 476 patients with hepatocellular carcinoma (HCC) who received LENVIMA in REFLECT, 44% were ≥65 years of age and 12% were ≥75 years of age. No overall differences in safety or effectiveness were observed between patients ≥65 and younger subjects. Patients ≥75 years of age showed reduced tolerability to LENVIMA. 

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

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

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

OVERDOSAGE Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.
YEAGER: The fact that he now has a del(17p) abnormality and has had prior therapies with similar mechanisms of action would be 2 things that make me favor belantamab. But given his rural residence and previous autologous transplant, follow-up and close monitoring give me some concerns.

MCKENNEY: I think of the same factors that Dr Yeager mentioned. He appears to be developing more resistant disease to the IMiDs [immunomodulatory imide drugs], and the transplant is increasing cells with del(17p), so I was going more directly to the BCMA [B-cell maturation antigen]-directed therapy.

MANASANCH: Would you consider, for example, belantamab mafodotin [Blenrep] as an infusion given every 3 weeks? Sometimes we give it less frequently vs carfilzomib [Kyprolis], which is [given] at minimum once a week. Do you think that could influence your decision in a patient like this?

MCKENNEY: Yes, he is going to need more targeted treatment. He has had the IMiDs and is becoming more refractory to that treatment.

REDDY: I did not choose belantamab because we do not have good support. I do not have an ophthalmologist [the patients] are going to see every 3 weeks. Sometimes we give it less frequently vs carfilzomib [Kyprolis], which is [given] at minimum once a week. Do you think that could influence your decision in a patient like this?

MCKENNEY: Yes, he is going to need more targeted treatment. He has had the IMiDs and is becoming more refractory to that treatment.

REDDY: I did not choose belantamab because we do not have good support. I do not have an ophthalmologist [the patients] are going to see every 3 weeks. Sometimes we give it less frequently vs carfilzomib [Kyprolis], which is [given] at minimum once a week. Do you think that could influence your decision in a patient like this?

MANASANCH: I am sorry you do not have the option to give belantamab in your practice, but for a patient like this, you could do carfilzomib with cyclophosphamide [Cytoxan], and as the patient is progressing on daratumumab, you could always switch to isatuximab-irfc [Sarclisa]. But they are similar antibodies.

Selinexor [Xpovio] could be another option. There are no head-to-head comparison studies. What would the efficacy be? The toxicity of carfilzomib and selinexor may be a little more overall than just belantamab, especially if you monitor the patient [who receives belantamab] and have the ophthalmologist do assessments. We do not see a lot of toxicity. Of course, there are other treatment options you could select, but belantamab would be a good option for this patient at this stage of their treatment. So what do you think if the patient had cataracts? Would this affect you giving belantamab [to] this patient?

YEAGER: If they had cataract surgery, they have an implantable lens. It is not biologic, and the keratopathy [associated with belantamab] is not lenticular in nature, is it? So I would [suggest] ophthalmologic evaluation and close ophthalmologic follow-up. But I stand to be corrected on this because I do not have as much experience with belantamab. I do not think that cataracts would be an absolute contraindication.

MANASANCH: Yes, that is correct. Cataracts are very common in [patients with] multiple myeloma because they receive dexamethasone. Cataracts are like sores for myeloma, and patients get a lot of them. This is a real issue, but it is very easy to have the cataracts removed and new lenses implanted. The patient could have cataract surgery before and then proceed to belantamab without any problems.

GOROUHI: If you have a patient who had 4 different classes of medication, is belantamab the only option left? Because it is recommended for patients with more than 3 prior treatments [based on the NCCN (National Comprehensive Cancer Network) guidelines].

MANASANCH: Well, one could use any of the recommended medicines the patient has not received. So everything not used in the prior lines could still be used. Belantamab is usually for late relapses [and] is considered after 3 prior therapies, but you could give it after a second relapse. But you would not be able to give idecabtagene vicleucel [Abecma] or ciltacabtagene autoleucel [Carvykti] for a second relapse because their approval is for patients with 4 prior lines of therapy. So the patient would have had an anti-CD38 antibody, a PI [proteasome inhibitor], and an IMiD.

YEAGER: I think it is important that these are guidelines. We like consistency, but we appreciate that there is a uniqueness to patients in these guidelines for late relapse therapies. We need not be limited to what is listed in the guidelines. We must be sensitive to that.

DISCUSSION QUESTIONS

- If you have used belantamab, what has your experience been? If you have not used it, what are your perceptions of it?
- Have you used selinexor-based treatment? What were your experiences with it?

YEAGER: Because my practice is largely limited to transplant, I have sent patients back to their primary...
oncologist [whether] they were referred [to me] for transplant or had a transplant with progression of myeloma, and we might make recommendations for therapies including belantamab. That is why I do not have direct experience.

MCKENNEY: I have not had a patient who has been an appropriate candidate [for belantamab] because they are still on IMiDs and PIs. But we do have ophthalmologists, and we would not be opposed to using it; we just have not had the right patient.

GOROUHI: When my patient gets to the significant level of refractory or relapsed disease, I usually get a second opinion from The University of Texas MD Anderson Cancer Center or a similar organization. For my last patient, [the center] suggested the next line of treatment be the clinical trial option. There is 1 trial that is not FDA approved, so we have not started it. So far I have not had a patient for whom belantamab was suggested, and I have not had that opportunity to start, but I am not against it. If there is a case that is indicated, I am for it.

REDDY: As I commented earlier, we do not have an ophthalmologist. I have found one who is interested to see patients [who receive belantamab]. Maybe with the next patient who meets these criteria I will probably use it, but...it is one thing to have cytopenia or cardiac adverse [events] [AEs], but ophthalmologic ones scare me. If I had other options, I would prefer not to go there.

CHU: I have the same impression. Because of the eye-related AE, I had to coordinate with the ophthalmologist, and sometimes it gets the treatment delayed. I do not think it is more toxic than the other ones, but it will put a damper on my enthusiasm.

MANASANCH: Have you used selinexor-based treatment for relapsed/refractory multiple myeloma? If so, can you share how that went?

GOROUHI: I currently have a patient on this medication. The consultant who gave us the second opinion asked us [whether] the patient was heavily treated before and was weak. [Based on this] he asked me to start from the second dose reduction. He said that if you can go up on that, then you can try. I started the medication, and the patient was tolerating it, so I went 1 dose up and then another dose up. Then the patient was feeling bad, so we eventually had to go down to the same dose originally requested. He is tolerating that dose and we [have] had a great response so far.

Interestingly, the physician who sent the patient to me was under the impression it was not going to work. He was [preparing to enroll him in] a clinical trial after that, but when I told him how good the response was, he crossed that out.

MANASANCH: Good. I am happy for the patient.

REDDY: I have used [selinexor] only once. It was a couple [of] years ago, but this patient had already received all other drugs. We [used selinexor] for 1 or 2 months, but he [died]. It was the last attempt.

DISCUSSION QUESTIONS

• What do you view as the pros and cons of using belantamab mafodotin?
• How does this compare with selinexor-based treatment in this setting?
• What are the goals of therapy for patients who have been heavily pretreated for multiple myeloma?
• How important is quality of life?

YEAGER: It is about the AEs and their frequency, and that includes the treating physician’s and patient’s willingness to tolerate them. I realize there are other AEs that occur...
with sufficient frequency in patients receiving selinexor. [With] keratopathy being the main concern of belantamab, knowing one can have these dose delays without a pronounced loss of effect indicates to me that there is good tolerability. I realize the comparison of belantamab vs selinexor in terms of efficacy, responses, duration of response, OS [overall survival], and PFS [progression-free survival] is a large discussion [From the Data].

MANGAT: Belantamab looks effective, but we must deal with the obvious visual toxicities compared with selinexor, which is presumably more convenient orally. But I am sure it comes with its own AEs like neurotoxicity and hyponatremia. So you must weigh the AEs and discuss with patients to see what they are willing to tolerate, and we can manage [AEs] along the way.

REDDY: Based on the mechanism [of action], this is a different drug compared with the 3 other classes of drugs, which is exciting. Only 3% of patients had toxicities that caused discontinuation. But the [high rate of] grade 3 toxicity of keratopathy...is my concern.

MANASANCH: That is a valid concern. Does anyone else have this concern as well, knowing the keratopathy [is not necessarily] symptomatic and [can be] resolved? In my experience, because I have given a lot of belantamab to 30 patients or so, it is well tolerated. We usually do not see high-grade keratopathy suddenly; it is gradual. So if you reduce the dose and follow the patients, you do not need steroids. It is very well tolerated. They can get visual changes, but it is reversible. Most patients do not have visual changes, so you must monitor them and be careful, but that has been my experience.

MANASANCH: I would say 4 months or so. I have a patient who [participated in] the DREAMM 2 study [NCT03525678], and he has been on belantamab mafodotin for more than 3 years, [considering] this study is from 2019 or 2018. I delayed treatment for 3 or 4 months. He [left] the study because they closed it, but he is still on belantamab. It has been a long time, [approximately] 3 to 4 years. I have a couple of patients who have been on it for a long time. They are doing well.

SUD: How long do you [normally] need to delay before you resume [treatment] after the [patient has] keratopathy?

MANASANCH: You can delay it 3 to 4 weeks. I have a patient who has been on it for 1 year, and I told them to come back in 6 weeks. We will check their eyes because I can tell based on how long it takes to resolve the keratopathy. But I have had patients who delayed treatment for 3 or 4 months, [and] they still have deep remissions. Many times, they can get good remissions. [As] with other chemotherapies, if the cell counts do not recover, we tend to discontinue treatment.

SUD: Do you ever decide to stop belantamab mafodotin if the patient does not have a resolution of the keratopathy from grade 2 to grade 1?

MANASANCH: Usually the patient comes in and they have grade 2 keratopathy, which is usually easy to resolve. Because you do not know when you check; it could be on the way to grade 3 or it could be resolving. But for most patients, [it takes] up to a couple of months to resolve. When they come back and [it is] not resolved, you have them come back the next month. After 2 or 3 months, it resolves, but myeloma could progress in the meantime, and you try to keep [withholding treatment]. If they are in remission, the myeloma is not worsening, and these patients feel great. For most who have visual changes, the visual changes seem to go away a little faster than keratopathy. But you can have them keep coming back until [the keratopathy resolves], and if you [need] a lot of [interruptions], then you reduce the dose or you extend the frequency of the infusions.

DISCUSSION QUESTIONS

• How do you see belantamab mafodotin fitting into the overall treatment plan for relapsed/refractory multiple myeloma?
• Would you consider using this agent in combination regimens?
MANASANCH: This drug [is in] a lot of trials right now, even a frontline study. What are your thoughts on using this medication in combination with [an agent like] pomalidomide? A trial with good data has been reported with pomalidomide. Do any of you have thoughts on whether you would use this in combination with other agents [for] myeloma?

YEAGER: I would like to see some preliminary data with combination therapies. We have discussed extensively how keratopathy might be a reason for delay or discontinuation of the agent. So I would like to know [whether] there could be additive toxicities. I would be interested in trials evaluating its use with other agents, but I would not be the one to empirically try combinations.

MCKENNEY: It seems belantamab has a relatively high AE rate, and when you add more drugs, you are going to increase the toxicity. With multiple myeloma, the push has been to give multiple agents as opposed to other solid tumors where you usually give a single agent, so I would want to see what the data show when used in combination. I would think the toxicity would be much worse.

MANASANCH: That is valid. The good thing with this agent is [no other agent it could be combined with is associated with] the keratopathy.

MCKENNEY: Right, no overlapping [toxicity].

MANASANCH: Yes, so what could get worse are thrombocytopenia and AEs like that, but because the toxicity profile is so different from other drugs [used for] myeloma, in combination it seems to be fine. We have used it with pomalidomide, and there are other combinations out there [in trials]. We will have to see what everything looks like, but I think it is a concern when you add other medicines in combinations.

REFERENCES

See more Case-Based Peer Perspectives at TargetedOnc.com/link/1001 for further insight on managing oncology-based patient cases.
INDICATION
XPOVIO® (selinexor) is a prescription medicine approved:

- in combination with bortezomib and dexamethasone (XVd) to treat adult patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION

Thrombocytopenia: XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma. Thrombocytopenia is the leading cause of dosage modifications. Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Monitor patients for signs and symptoms of bleeding. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

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

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

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

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

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

Monitor sodium level at baseline and throughout treatment. Monitor weight, nutritional status, and volume status at baseline and throughout treatment and provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

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

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

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity. Advise patients to refrain from driving and engaging in hazardous occupations or activities until the neurological toxicity fully resolves. Institute fall precautions as appropriate.
ADVERSE REACTIONS

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

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

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

Embryo-Fetal Toxicity: XVPOVIO can cause fetal harm when administered to a pregnant woman.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XVPOVIO and for 1 week after the last dose.

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

USE IN SPECIFIC POPULATIONS

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

Please see full Prescribing Information.

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

Reference: 1. XVPOVIO (selinexor) [prescribing information]. Newton, MA: Karyopharm Therapeutics Inc.; April 2021.
ADVERSE REACTIONS

**Premature closure of trial due to futility**

**Serious Infection**

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia. 69% of patients experienced any grade of infection. Grade ≥3 infections were reported in 32% of patients, and deaths from infections occurred in 3.1% of patients. The most frequently reported Grade ≥3 infection was pneumonia in 14% of patients, followed by sepsis in 4.1% and upper respiratory tract infection in 3.6%. Atypical infections reported after XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

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

**Neurological Toxicity**

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

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

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

**Embryo-Fetal Toxicity**

XPOVIO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

**Cataract**

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

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

**Multiple Myeloma**

**XPOVIO in Combination with Bortezomib and-Dexamethasone (SVD)**

The safety of XPOVIO in combination with bortezomib and dexamethasone was evaluated in BOSTON. Patients were randomized to receive XPOVIO 100 mg orally once weekly in combination with bortezomib and dexamethasone (SVD) (n=195) or bortezomib and dexamethasone (Vd) (n=204). Among patients who received XPOVIO, the median duration of XPOVIO treatment was 29 weeks (range: 1 to 120 weeks) and the median dose was 80 mg (range: 30 to 137 mg) every week.

Serious adverse reactions occurred in 52% of patients who received XPOVIO in combination with bortezomib and dexamethasone. Serious adverse reactions in >3% of patients included pneumonia (14%), sepsis, diarrhea and vomiting (4% each). Fatal adverse reactions occurred in 6% of patients within 30 days of last treatment, including pneumonia (n=3) and sepsis (n=3).

Grade ≥2 peripheral neuropathy, a pre-specified key secondary endpoint, was lower in the SVD arm (21%) compared to the Vd arm (34%); odds ratio 0.50 (95% CI: 0.32, 0.79). The median treatment duration was 30 weeks (range: 1-120 weeks) in patients who received once weekly Svd as compared to 32 weeks (range: 1-122 weeks) in patients who received twice weekly Vd.

Permanent discontinuation of XPOVIO due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation of XPOVIO in ≥2% of patients included fatigue (3.6%), nausea (3.1%), thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting (2.1% each).
Table 5: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received XPOVIO in Combination with Bortezomib and Dexamethasone (SVD) with a Difference Between Arms of >5% Compared to Vd in BOSTON

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Weekly SVD (n=195)</th>
<th>Twice Weekly Vd (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>4.1</td>
</tr>
<tr>
<td>General Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>59</td>
<td>28</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite decrease</td>
<td>35</td>
<td>3.6</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>26</td>
<td>2.1</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathyb</td>
<td>33</td>
<td>4.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>29</td>
<td>3.6</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Vision blurredc</td>
<td>13</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Key: a. Fatigue includes fatigue and asthenia.

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose (see Dose). Advise pregnant women of the risks to a fetus.

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

Data

Animal data

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor at 0, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve (AUC) at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

Lactation

Risk Summary

There is no information regarding the presence of selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with XPOVIO and for 1 week after the last dose.

Females and Males of Reproductive Potential

XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose (see Dose). Advise pregnant women of the risks to a fetus.

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

Dosing Instructions:

- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to swallow the tablet whole with water. The tablet should not be broken, chewed, crushed, or divided.
- Advise patients that if a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of XPOVIO, advise them to take the next dose on the next regularly scheduled day.
- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to take their prescribed dexamethasone (if applicable) and prophylactic anti-nausea medications exactly as directed.
- Advise patients that blood tests and body weight will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first three months of treatment.
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment.

Hematologic Adverse Reactions

Thrombocytopenia

Advise patients that they may develop low platelet counts (thrombocytopenia). Advise patients that thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

Gastrointestinal Adverse Reactions

Advise patients that they may experience nausea/vomiting and diarrhea and to contact their physician if these adverse reactions occur or persist.

Advise patients that they may experience weight loss or decreased appetite.

Advise patients to report signs of bleeding right away.

Anemia

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia.

Neutropenia

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

Serious Infection

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever).

Neurotoxicity

Advise patients that they may experience confusion and dizziness. Advise patients to report symptoms of neurological toxicity right away. Advise patients not to drive or operate hazardous machinery until the neurological toxicity fully resolves. Advise patients to use fall prevention measures as warranted.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to contact their healthcare provider of a known or suspected pregnancy.

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

Cataract

Advise patients of the potential risk of worsening or new onset of cataract, that may require surgery. Advise patients to readily inform their healthcare professionals of changes in vision (i.e. blurred vision) and that ophthalmologic evaluation may be performed as clinically indicated.

Fatigue

Advise patients that they may experience fatigue.

Lactation

Advise women not to breastfeed during treatment with XPOVIO and for 1 week after the final dose.

Concomitant Medications

Advise patients to take 5-HT3 antagonist prophylactic treatment and other anti-nausea agents prior to and during treatment with XPOVIO.

Advise patients to speak with their physician about other medications they are currently taking and before starting any new medication.

For more information, call 1-888-209-9326 or go to www.XPOVIO.com.

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US-XPOV-01/21-00020 (05/21)
TUMOR LYSIS SYNDROME

Mato Examines Tumor Lysis Syndrome Risk and Hyperuricemia Management

CASE

- A 76-year-old man presented with fatigue, weight loss, drenching night sweats, and a fever.
- Medical history: Hypertension, hypercholesterolemia, atrial fibrillation, hypothyroid, gastrointestinal bleed/hiatal hernia, anemia, all controlled with medication:
  - Aspirin 81 mg once daily, pantoprazole 40 mg twice daily, ferrous sulfate 325 mg once daily, atorvastatin 40 mg once daily, levothyroxine 100 µg once daily, metoprolol 25 mg twice daily
- Physical examination: spleen palpable approximately 8 cm below costal margin
- CT: 4-cm bilateral axillary nodes, numerous 2-cm-to-3-cm nodes in retroperitoneum and bilateral inguinal regions

Molecular testing/fluorescence in situ hybridization:
- IGHV unmutated
- TP53 wild type

Diagnosis: stage IV chronic lymphocytic leukemia (CLL)
- International Prognostic Index score: 4

Targeted Oncology™: What is the pathophysiology of tumor lysis syndrome (TLS)?

MATO: TLS is considered a potential life-threatening oncologic emergency. It is a cascade of pathophysiological events initiated when tumor cells are rapidly destroyed, either spontaneously or in the setting of treatment, that can lead to multiorgan failure. The major concerns are renal dysfunction, cardiac dysfunction, [and] neurological dysfunction, all of which can lead to sudden death.1

The rapid destruction of cells can lead to expelling of their intracellular contents into the bloodstream and one can develop abnormalities including hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and uremia or renal dysfunction.1

The consequences of these electrolyte abnormalities—for example, the efflux of potassium, an important intracellular cation—can lead to hyperkalemia that can directly cause dysrhythmia. That’s probably the most concerning one that we see in patients when we have effective cancer-directed therapies. Of course, you can also have release of nucleic acids directly related to purine catabolism and that can subsequently lead to precipitation of uric acid crystals, leading to acute renal failure. Subsequently, acute renal failure can lead to electrolyte abnormalities like hyperkalemia. They’re all interconnected.

Renal failure can also be secondarily caused by calcium phosphate crystal deposition as well, which can also lead to hyperkalemia and cardiac dysrhythmia. Hyperphosphatemia can also lead to hypocalcemia with intratissue crystallization of calcium phosphate crystals, which can have neurological consequences. Taken together, it’s not just 1 abnormality, but each of these

<table>
<thead>
<tr>
<th>Laboratory Results</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (WBC)</td>
<td>105,000 × 10^3/µL (90% lymphocytes; &gt; 2 × upper limit of normal [ULN])</td>
</tr>
<tr>
<td>Platelets</td>
<td>125 × 10^3/µL (high, 400 × 10^3/µL ULN)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>370 U/L (high, 280 U/L ULN)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.8 g/dL (low, 12.1 g/dL lower limit of normal)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>10.8 g/dL (low, 12.1 g/dL lower limit of normal)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>39 mL/min</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate</td>
<td>6 g/dL (13.5-17.5)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>200 mg/dL (0.57-2.63)</td>
</tr>
<tr>
<td>albumin</td>
<td>3 g/dL (IgA λ)</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>3.4 g/dL (3.3-5.7)</td>
</tr>
</tbody>
</table>

Anthony Mato, MD, MSCE
Director, CLL Program
Memorial Sloan Kettering
Cancer Center
New York, NY

74 Case-Based Roundtable Meetings Spotlight
electrolyte abnormalities can play into one another to magnify and worsen the outcome for patients.

**How is risk assessed for TLS? What are some risk factors?**

Patients are stratified based on TLS risk, high risk being defined as greater than 5% risk, intermediate being 1% to 5%, and low risk being less than 1%. The breakdown focuses on the different lymphomas and leukemias and how to determine what the risk of TLS is. For example, CLL is not defined as high risk, although I might argue that patients with extremely bulky disease who were treated with very sensitive therapies would be considered high risk, but certainly the use of biologic or targeted agents in CLL puts patients at an intermediate risk for TLS, particularly the targeted therapies. Each tumor type—be it Burkitt lymphoma, acute lymphocytic leukemia [ALL], or acute myelocytic leukemia [AML], high [WBC] counts, high LDH, bulky disease, and lymphadenopathy—will elevate patients into either an intermediate-risk or a high-risk category.

The risk factors for TLS are broken down into the 3 categories of disease risk factors, patient-related factors, and treatment-related factors. Disease risk factors include rapid cellular proliferation, potentially marked as elevated LDH; high tumor burden, so bulky tumors with an elevated WBC count; sensitivity to cyto reductive therapy, probably one of the most important ones because the better the therapies we have, the faster acting they are and the more likely the body is overcome by the electrolyte intracellular contents; renal infiltration or outflow tract obstruction by tumor; bone marrow involvement, again as a measure of bulk of disease; and splenomegaly as a measure of bulk of disease.

The patient-related factors are preexisting factors like renal dysfunction and uremia, for example. If your kidney is not great to begin with, of course that’s a problem. Other factors include if patients have pretreated hyperuricemia or hyperphosphatemia, particularly in the setting of spontaneous TLS; hypovolemia or hypotension; acidic urine, which would facilitate crystallization of uric acid; congestive heart failure; and older age.

The treatment-related factors include the intensity of the cyto reductive therapy, whether you’re giving 1 agent or combination, and this is disease specific according to the tumor type; inadequate hydration during cyto reductive therapy—I just got a call about a patient whose uric acid was up a little bit, so I gave them a bolus of fluids; and the concurrent use of nephro toxic drugs.

To me, any Burkitt lymphoma has an incredibly high risk for TLS. This is sort of the textbook scenario where patients present with spontaneous TLS or TLS with glucocorticoids requiring dialysis before they start therapy. I think in pediatrics they would have a dialysis catheter placed before they began Burkitt-specific therapy because the risk was so high.

In ALL and AML, particularly with a high WBC count, there’s a connection between the degree of leukocytosis and TLS risk. Lymphoblastic lymphoma with an elevated LDH, T-cell leukemia, or lymphoma [are high risk too]. I think diffuse large B-cell lymphoma [DLBCL] is intermediate risk, but the risk is particularly higher if the LDH is elevated or there’s bulky disease. Mantle cell lymphoma in the leukemic phase of the disease with elevated LDH and bulky tumor is high risk. CLL with bulky disease as evidenced by enlarged lymph nodes, spleen and/or an elevated lymphocyte count is high risk, particularly if you’re using CD20-directed antibodies such as venetoclax [Venclexta].

Of course, one can see TLS with any of the therapies including radiation or steroids, but cytotoxic chemotherapy is probably the most common cause and includes agents like bendamustine [Treanda]; blinatumomab [Blinicyto]; bortezomib [Velcade]; carfilzomib [Kyprolis]; dasatinib [Sprycel]; doxorubicin [Adriamycin]; ibrutinib [Imbruvica], which I would consider probably low risk; lenalidomide [Revlimid]-based therapy; methotrexate; obinutuzumab [Gazyva], which I would consider high risk; vincristine [Oncovin]; and rituximab [Rituxan].

**How is TLS defined and diagnosed?**

There is a distinction between clinical and laboratory TLS as per the Cairo-Bishop classification. I’ve already touched on the intrinsic tumor-related risk factors such as high cell proliferation rate, high-risk cancers, large tumor burden, chemosensitivity, and the patient-related factors including pretreatment electrolyte and/or renal dysfunction, preexisting nephropathy, oliguria, acidic urine, nephrotoxins already on board, and inadequate hydration.

The definition of TLS can be broken down into 2 components, laboratory and clinical. Laboratory TLS requires 2 or more of the following abnormalities within 3 days prior to or up to 7 days after the initiation of a cytotoxic therapy. The cutoffs are uric acid greater than or equal to 8 mg/dL; potassium greater than or equal to 6 mEq/L; phosphate greater than or equal to 6.5 mg/dL for children, but a little bit lower threshold for adults at 4.5 mg/dL; calcium less than or equal to 7 mg/dL; or a 25% change from baseline in any of the above.

As an example, in the patient about whom I got a call, the nurse said to me the potassium is normal at 4.2 mEq/L, but to me that’s not super helpful. I also want to know what the baseline was. If they started out at 3.2 mEq/L, that’s a problem. If they started out at 4.1 mEq/L, that’s not a problem. You also need to look for trends.

Clinical TLS can occur in any patient with laboratory TLS plus 1 or more of the following: creatinine 1.5 times...
the upper limit of normal, which is an immediate change; cardiac arrhythmia; seizure; or sudden death. Outside of the creatinine bump, the other abnormalities that define clinical TLS are considered life threatening.

What is the rationale for hypouricemic therapy?
Allopurinol (Zyloprim), for example, interferes with purine metabolism and inhibits xanthine oxidase. Normally when you think about purine catabolism, the end point is uric acid, which is a poorly soluble end product that can easily precipitate in the kidney. I think we’re the only mammalian species [that doesn’t] have urate oxidase, which is the rasburicase [Elitek] product.

All other mammals will degrade uric acid to allantoin, which is soluble and easily excreted in the urine, but we don’t have that, so that’s where rasburicase comes into play. It’s an infusion enzyme [that] can break down uric acid in the bloodstream to allantoin, which is then easily excreted in urine.

I don’t fully understand why from an evolutionary perspective, but we somehow lost our ability to break down uric acid. Of course, hyperuricemia leads to renal dysfunction including uric acid nephropathy, nephrocalcinosis, obstructive nephropathy, and xanthine nephropathy, which is due to allopurinol therapy, so it is a consequence of the preventive strategy for TLS.4,6

Hyperuricemia can lead to secondary hypocalcemia, which causes renal failure, seizures, and then dysrhythmia. Hypocalcemia can make [patients] quite sick. One can also have electrocardiogram [ECG] changes, dysrhythmia, paresthesia, muscle cramps, and tetany. Hyperkalemia, which I think we understand best, can change the ECG and can cause dysrhythmia, paresthesia, weakness, and myalgias.4,6 There are a lot of different clinical issues here, but we’re focusing on how to intervene in 1 problem, which is hyperuricemia that can lead to renal dysfunction.

The prevention guidance for TLS is stratified by the estimated risk for an event. Low risk is less than 1%, and the strategy is watch and wait, which may be appropriate, although you should still think about vigilant monitoring of laboratory parameters and fluid status and having a low threshold for IV [intravenous] fluid infusion and allopurinol prophylaxis.4,6 I think for most of the diseases we’re talking about, we’re comfortable starting allopurinol and providing IV fluids including in leukemias and high-grade lymphomas regardless of the risk.

Intermediate risk is 1% to 5% risk. One is supposed to do aggressive IV hydration of approximately 3 L/m² per day. This essentially results in patients getting 1.5 L to 3 L of IV fluids daily. Other prophylactic strategies include allopurinol and vigilant laboratory monitoring. Rasburicase can be thought about as an initial hypouricemic agent in place of allopurinol, particularly in certain patients.2,4

High risk is a risk of greater than 5%. Fluids are given aggressively. One might want to think of prophylactic rasburicase as the standard of care. Of course, you must make sure the patient is not G6PD deficient before you do that. Do vigilant monitoring of laboratory values and fluid status. Allopurinol can be substituted for rasburicase if the patient is G6PD deficient.5,6 Hydration is most important. It trumps any of these drugs. If you hydrate a patient well, you’re going to dilute the electrolytes and cause increased urine output, excreting electrolytes more effectively and minimizing crystallization.

The IV fluid dose for high-risk TLS is generally normal saline at 2500 mL/m²/d to 3000 mL/m²/d. Never alkalize the urine. It’s malpractice. The individual patient’s tolerance and comorbidities must be taken into consideration. Obviously, you’re not going to give 3 liters to a patient who’s in heart failure or a patient who’s on dialysis when they’re not due for dialysis at that time. Consider the medical history. Normal saline is the mainstay of hydration, not Lactated Ringer’s solution, and not alkalized fluid, which will cause precipitation of calcium phosphate in the kidneys and kidney failure.2,4

What data support the use of rasburicase as an antihyperuricemic agent?
There was an interesting study [NCT00230178] of more than 180 patients who received either weight-based rasburicase for 5 days, rasburicase and allopurinol combined, or allopurinol as a monotherapy.

Anticancer therapy was initiated 4 hours to 24 hours after the first antihyperuricemic agent dose and then patients were stratified by their risk for TLS.7 Participants in this study had to be adults; have an ECOG performance status of up to 3, so they could have some poor performance status; have acute leukemia or lymphoma; or be at high risk of TLS. The primary end point of the study was lowering of uric acid, so this was not meant to be a trial with a clinical end point but a laboratory end point. There’s an intent-to-treat group, a high-risk group, and a hyperuricemic group. The rasburicase monotherapy strategy was probably the most effective at lowering hyperuricemia, followed by the combination, then the allopurinol monotherapy.

There’s a dramatic reduction in uric acid values in either of the arms where the rasburicase was included, but not so great for allopurinol, even if this was started a few days before the initiation of the anticancer therapy. The lowest rate of hyperuricemia, as one would predict, was with the rasburicase followed by the combination, and then the allopurinol as a monotherapy [Figure]. Interestingly, this didn’t translate into a difference in clinical TLS. It was 3% vs 4% vs 3%, for the rasburicase,
allopurinol monotherapy, and combination arm, respectively. But the rasburicase monotherapy did result in a lower rate of laboratory TLS of 21% vs 41% for allopurinol vs 27% for the combination.

For laboratory TLS, one must have 2 or more abnormalities to meet the definition. So hyperphosphatemia or hyperuricemia by itself is not enough. By minimizing the hyperuricemia, you’re essentially removing that as a variable and that decreases the laboratory events. None of these strategies translated into a very high risk of clinical TLS, thankfully, so they were all effective in that regard. Of course, we don’t know the management per se for each of these arms and whether it was different in the setting of these electrolyte abnormalities, but it didn’t translate into a difference in clinical TLS.

Acute renal failure was a little bit higher in the combination arm at 5% vs 2% for the other arms. Renal failure or renal impairment was a little bit higher in the combination arm at 9% vs 4% for rasburicase alone vs 2% for allopurinol alone. The increase in creatinine was a little lower in the rasburicase arm at 8% vs 10% for the other arms, although I doubt this has any statistical significance.

The drug-related adverse events [AEs] were 4% in the rasburicase arm vs 5% in the allopurinol arm and 1% in the rasburicase to allopurinol arm. This is interesting to me because I would have thought allopurinol was even more toxic than this. In my own practice I have seen issues with skin such as rash, and I see liver dysfunction quite frequently, but it wasn’t seen here as frequently as I would have expected. I think the take-home from this is that all of these were well tolerated, and AEs were relatively rare.

**When should a physician consider prophylaxis for TLS?**

Based on the NCCN [National Comprehensive Cancer Network] B-cell lymphoma guidelines for TLS, one should consider prophylaxis for patients with the following risk factors: Burkitt or lymphoblastic lymphoma, and occasionally DLBCL; anyone who presents with spontaneous TLS; elevated WBC count, meaning leukemic-phase disease; bone marrow involvement, meaning stage IV disease; preexisting elevated uric acid; ineffectiveness or intolerance of allopurinol; and renal disease or renal involvement by tumor.

TLS is best managed if anticipated and treatment is started prior to chemotherapy and the centerpiece of treatment includes vigorous hydration and management of hyperuricemia, frequent monitoring of electrolytes, and aggressive correction of electrolyte abnormalities.

**How is TLS prophylaxis used in patients being treated with venetoclax?**

Venetoclax is indicated in AML and CLL. The WBC count should be less than $25 \times 10^9/L$ prior to venetoclax initiation and one might want to use cytoreduction to get a patient there. Prior to the first dose you should give prophylaxis with adequate hydration and antihyperuricemic...
agents and continue during the ramp-up phase. Assess blood chemistry and correct preexisting electrolyte abnormalities.

The recommendations for monitoring blood chemistry for TLS are at predose, 6 to 8 hours after each dose, and 24 hours after final dose. For patients with risk factors, consider additional measures, including increasing the frequency of laboratory monitoring or reducing the starting venetoclax dose. In 2 different trials, the TLS rate after venetoclax is relatively low, at 1.1% (all laboratory TLS) and 5.6% (4 clinical events, 2 of which were deaths). But this is not a regimen that’s immune from risk of life-threatening TLS.

The NCCN guidelines for TLS monitoring for inpatient treatment strongly recommend doing it during cycle 1, especially through dose escalation. Patients may need hospitalization even beyond cycle 1. There are recommendations as per label, whether you’re giving venetoclax with a hypomethylating agent or low-dose cytarabine during the dose escalation. The recommendation is treatment with allopurinol or other uric acid–lowering agents until no further risk.

For proliferative disease, monitor blood chemistry every 6 to 8 hours. If within the normal limits, recheck once daily and continue monitoring. After the first several days if you think the risk is lower, you can back off on the frequency of the laboratory monitoring, and then aggressively monitor and manage electrolyte imbalances.

There are NCCN guidelines for TLS prophylaxis in CLL, which has not been considered a big deal from a TLS perspective historically. However, because of the rapid responses with agents like venetoclax, it’s now an issue. Prophylaxis should be considered for patients receiving venetoclax, chemoimmunotherapy, lenalidomide, or obinutuzumab; patients with progressive disease after a small molecule inhibitor; bulky lymph nodes; spontaneous TLS; tuzumab; patients with progressive disease after a small lymphocytic lymphoma with the 5-week ramp-up is relatively low, at around 5%, but certainly 2% to 3% for each trial. Most of these events are laboratory events. In the escalated 2-week-to-3-week ramp-up, there’s a 13% risk.

The TLS rate in clinical trials for venetoclax in CLL or small lymphocytic lymphoma with the 5-week ramp-up is relatively low at around 5%, but certainly 2% to 3% for each trial. Most of these events are laboratory events. In the escalated 2-week-to-3-week ramp-up, there’s a 13% risk. There are very few patients with CLL who must have an escalated ramp-up due to concern of clinical proliferative disease.

**POLLING QUESTION**

At a live virtual event, Mato asked participants, “Would you initiate TLS prophylaxis for this patient in the described case of CLL?”

- Yes, hydration, monitoring, and allopurinol 71% (10)
- Yes, hydration, monitoring, and rasburicase 29% (4)
- No, I would watch and wait 0% (0)
- Yes, hydration and monitoring 0% (0)
- Other 0% (0)

Total votes: 14

**LISTEN IN**

Targeted Oncology™ presents Targeted Talks, a monthly podcast featuring academic and community oncologists discussing the latest advances and best practices for patient care, available here:
Dosing and Toxicity: Management of Lenvatinib for Patients With Advanced HCC

CASE SUMMARY

A 77-year-old White woman presented to her primary care physician complaining of abdominal pain and fatigue. She had cirrhosis due to heavy alcohol use; Crohn disease, controlled with infliximab (Remicade); and a history of variceal bleeding, with banding 2 months ago. She had an ECOG performance status of 1. A CT scan of the chest, abdomen, and pelvis with triphasic liver evaluation revealed a 4.5-cm LR5 hepatic mass in the right lobe and metastatic disease in the lung. She had a Child-Pugh status of A. Her α-fetoprotein level was 380 ng/mL. Biopsy was obtained and confirmed the diagnosis of hepatocellular carcinoma (HCC).

POLLING QUESTION

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

- Atezolizumab + bevacizumab: 50% (4)
- Lenvatinib: 38% (3)
- Pembrolizumab: 12% (1)
- Sorafenib: 0% (0)
- Durvalumab: 0% (0)
- Other: 0% (0)

Total votes: 8

CASE UPDATE

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

FINN: This patient started on lenvatinib 12 mg daily. Lenvatinib is dosed by weight. Patients who weigh more than or equal to 60 kg get 12 mg.1 Patients weighing less than 60 kg get 8 mg. These doses are lower than [those] used in kidney cancer and thyroid cancer.

This patient has weight loss and is dose reduced to 8 mg and is referred to...nutrition therapy. Weight loss and loss of appetite are probably 2 of the most common adverse events [AEs] we see with the drug [Figure 12]. At 16 weeks, [she does] have a PR. Keep in mind, while most of the tyrosine kinase inhibitors [TKIs] have single-digit objective response rates [ORR], lenvatinib is the one TKI that had double-digit RECIST ORR.2

After 8 months of being on treatment, lenvatinib is discontinued for disease progression.

continued on page 87
IMFINZI + EP: The only IO combination with 3-year overall survival in 1L ES-SCLC

NCCN CATEGORY 1, PREFERRED

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

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

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

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

**Immune-Mediated Adverse Reactions**
Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions.

Please see Brief Summary of complete Prescribing Information on adjacent pages.
IMFINZI + EP: Sustained overall survival benefit at 3 years¹

**OVERALL SURVIVAL AT 3-YEAR PLANNED EXPLORATORY ANALYSIS**

(median duration of follow-up 39.4 months)

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<th>Time from randomization (months)</th>
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**Number of patients at risk**

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<tr>
<td>EP</td>
<td>269</td>
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</table>

**HR=0.71**

(95% CI, 0.60-0.86)

**SUPERIOR OVERALL SURVIVAL AT INTERIM ANALYSIS**²⁻⁶

**13-MONTH mOS**

WITH IMFINZI + EP

**10.3-MONTH mOS**

WITH EP ALONE

**HR=0.73**

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

**Safety and tolerability**

- Serious adverse reactions occurred in 31% of patients receiving IMFINZI + EP at the interim analysis and in 33% of patients receiving IMFINZI + EP at the 3-year analysis¹⁻³
- The most frequent serious adverse reactions reported in ≥1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and chronic obstructive pulmonary disease (1.1%)³
- The most common adverse reactions (occurring in ≥20% of patients) were nausea, fatigue/asthenia, and alopecia³
- Discontinuation rates were the same with IMFINZI + EP and EP alone (9% in both arms)⁴
- The most frequent serious adverse reactions reported in ≥1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and chronic obstructive pulmonary disease (1.1%)³
- Discontinuation rates were the same with IMFINZI + EP and EP alone (9% in both arms)⁴
- Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI + EP. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients)³

**HR=hazard ratio; CI=confidence interval; mOS=median overall survival; OS=overall survival; Q3W=once every 3 weeks; Q4W=once every 4 weeks.

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

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

**Immunomediated Adverse Reactions (continued)**

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

**Immunomediated Pneumonitis**

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

**Immunomediated Colitis**

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

**Immunomediated Hepatitis**

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

**Immunomediated Endocrinopathies**

- **Adrenal Insufficiency**: IMFINZI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

- **Hypophysitis**: IMFINZI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated. Grade 3 hypophysitis/hypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI.

- **Thyroid Disorders**: IMFINZI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hyperthyroidism or institute medical management of hyperthyroidism as clinically indicated.

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

- **Hypothryoidism**: IMFINZI can cause immune-mediated hypothyroidism. The incidence of hypothyroidism was 2.1% (39/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

- **Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis**: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Grade 3 immune-mediated type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI.

**Immunomediated Nephritis with Renal Dysfunction**

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

**Immunomediated Dermatology Reactions**

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

**Other Immunomediated Adverse Reactions**

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

- **Cardiac/vascular**: Myocarditis, pericarditis, vasculitis.

- **Nervous system**: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis...

**Adverse Reactions**

- **Injection site reactions**

**Immunotherapy and CAR-T Cell Therapy**

- **Immunotherapy**

**Monoclonal Antibody Therapy**

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

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

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

• **Endocrine**: Hypoparathyroidism

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

### Infusion-Related Reactions

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

### Complications of Allogeneic HSCT after IMFINZI

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

### Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI.

### Lactation

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

### Adverse Reactions

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

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

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

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

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

### References

IMFINZI® (durvalumab) injection, for intravenous use

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

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

DOSEAGE AND ADMINISTRATION
Recommended Dosage
The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with chemotherapy are presented in Table 1 (See Clinical Studies (14) in the full Prescribing Information).

IMFINZI is administered as an intravenous infusion over 60 minutes.

Table 1. Recommended Dosages of IMFINZI

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

Recommended IMFINZI dosage is based on the body weight of patients. Patients with a body weight of 30 kg are recommended to receive 1500 mg of IMFINZI, while patients with a body weight of less than 30 kg are recommended to receive 20 mg/kg of IMFINZI. IMFINZI is administered as an intravenous infusion over 60 minutes.

Dose Modifications for Adverse Reactions
No dose reduction for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. Dose modifications for IMFINZI in adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2. Recommended Dose Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-Mediated Adverse Reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Grade 2</td>
<td>Within 12 weeks of initiating corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>Within 12 weeks of initiating corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Colitis</td>
<td>ALT or AST increases to more than 3 times ULN or total bilirubin increases to more than 1.5 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>ALT or AST increases to more than 8 times ULN or total bilirubin increases to more than 3 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis with no tumor involvement of the liver</td>
<td>AST or ALT increases to more than 1 and up to 5 times ULN at baseline and increases to more than 5 and up to 10 times ULN or</td>
<td>Within 12 weeks of initiating corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>AST or ALT increases to more than 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>AST or ALT increases to more than 10 times ULN or total bilirubin increases to more than 3 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Grade 3 or 4</td>
<td>Within 12 weeks of initiating corticosteroids.</td>
</tr>
<tr>
<td>Neoplasms with RENAL Dysfunction</td>
<td>Grade 2 or 3 increased blood creatinine</td>
<td>Within 12 weeks of initiating corticosteroids.</td>
</tr>
<tr>
<td>Exfoliative Dermatologic Conditions</td>
<td>Grade 4 increased blood creatinine</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Suspected SJS, TEN, or DRESS</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Confirmed SJS, TEN, or DRESS</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Neurological Toxicities</td>
<td>Grade 2 or 3</td>
<td>Within 12 weeks of initiating corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

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

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

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

CONTRAINDICATIONS
None.

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

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after 6 cycles of IMFINZI therapy. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue IMFINZI depending on severity [See Dosage and Administration (2.2) in the full Prescribing Information]. In general, if IMFINZI requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. On improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

In Patients Who Did Not Receive Recent Prior Radiation
In patients who received IMFINZI on clinical trials in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 5 patients. Systemic corticosteroids were required in 19 patients (18/34) with pneumonitis who did not receive chemoradiation prior to initiation of IMFINZI.

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

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In Patients Who Received Recent Prior Radiation
The incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (30/163) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475) 11.1% were fatal and 2.7% were Grade 3 adverse reactions. Events resolved in 50 of the 87 patients and resulted in permanent discontinuation in 27 patients. Systemic corticosteroids were required in 64 patients (64/87) with pneumonitis who had received chemoradiotherapy prior to initiation of IMFINZI, while 2 patients required use of infliximab with high-dose steroids.

The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar when compared to patients with various cancers in a pooled data set or patients with ES-SCLC when given in combination with chemotherapy.

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

Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (>0.1%) and Grade 3 (0.4%) adverse reactions. Events resolved in 27 of the 37 patients and resulted in permanent discontinuation in 8 patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 2 patients (2/37) required other immunosuppressants (e.g., infliximab, mycophenolate).

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal
* Based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
** Resumed in patients with complete or partial resolution [Grade 0 to 1] after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.
† If ALT and AST are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue IMFINZI based on recommendations for hepatitis with no liver involvement.
Immune-Mediated Adverse Reactions

IMFINZI® (durvalumab) injection, for intravenous use

Cardiovascular:

Myocarditis, pericarditis, vasculitis.

Nervous System:

Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (myasthenic syndrome/myasthenia gravis crisis [exacerbation]).

Ocular:

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

Gastrointestinal:

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

Musculoskeletal and Connective Tissue Disorders:

Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthropathy, polymyalgia rheumatic.

Endocrine:

Hypoparathyroidism

Other (hematologic/malignant)

Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

Infusion-Related Reactions

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

Complications of Allogeneic HSCT after IMFINZI

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L-1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, transplant-associated cytomegalovirus disease (VOD) after reduced intensity conditioning, and steroid-refractory febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/L-1 blocking antibody prior to or after an allogeneic HSCT.

Emphysema: Fatal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fatal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased prematurity deliveries and premature neonatal death. Avoid pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI [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.

• Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1) in the full Prescribing Information]

• Infusion-Related Reactions [see Warnings and Precautions (5.2) 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 described in the Warnings and Precautions section reflect exposure to IMFINZI in 1889 patients from the PACIFIC study (a randomized, placebo-controlled study that enrolled 475 patients with Stage III NSCLC) and the CASPIAN study (N1080 [an open-label, single-arm, multicohort study that enrolled 670 patients with advanced solid tumors], and an additional open-label, single-arm trial that enrolled 444 patients with metastatic melanoma; an indication for which IMFINZI is not approved. In these trials, IMFINZI was administered at a dose of 10 mg/kg every 2 weeks. Among the 1889 patients, 38% were exposed for 6 months or more and 18% were exposed for 12 months or more. The data also reflect exposure to IMFINZI in combination with chemotherapy in 265 patients from the CASPIAN study (a randomized, open-label study in patients with ES-SCLC). In the CASPIAN study, IMFINZI was administered at a dose of 1500 mg every 3 or 4 weeks.

The data described in this section reflect exposure to IMFINZI in patients with ES-SCLC enrolled in the CASPIAN study.

Small Cell Lung Cancer

The safety of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was evaluated in CASPIAN, a randomized, open-label, multicenter, active-controlled trial. A total of 656 patients received IMFINZI (N = 328) or placebo (N = 328) with etoposide and either carboplatin or cisplatin for 4 cycles followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity. The trial excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants [see Clinical Studies (14.3) in the full Prescribing Information]. Among 265 patients receiving IMFINZI, 48% were exposed for 6 months or longer and 19% were exposed for 12 months or longer. Among 266 patients receiving chemotherapy alone, 57% of the patients received 6 cycles of chemotherapy and 8% of the patients received prophylactic cranial irradiation (PCI) after chemotherapy. IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. These include pneumonitis, hepatotoxicity, neutropenia, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each). Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%) and COPD (1.1%). Fatal adverse reactions occurred in 4.8% of patients receiving IMFINZI plus chemotherapy. These included pancytopenia (1.6%), septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients). The most common adverse reactions occurring in ≥20% of patients were nausea, fatigue/asthenia and alopecia.

Table 5 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 5. Adverse Reactions Occurring in ≥10% Patients in the CASPIAN study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough/Productive Cough</td>
<td>15.0</td>
<td>0.8</td>
<td>9.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>34.0</td>
<td>0.4</td>
<td>34.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>17.0</td>
<td>0.8</td>
<td>19.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.0</td>
<td>0.0</td>
<td>17.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.0</td>
<td>1.1</td>
<td>11.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>
IMFINZI® (durvalumab) injection, for intravenous use

Table 5. Adverse Reactions Occurring in ≥ 10% Patients in the CASPIAN study (cont’d)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism*</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>33</td>
<td>1.1</td>
<td>34</td>
<td>0.8</td>
</tr>
<tr>
<td>Rash†</td>
<td>11</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthma</td>
<td>32</td>
<td>3.4</td>
<td>32</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade3 or 4 (%)</th>
<th>Grade3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>4.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased AST</td>
<td>4.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>3.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1.5</td>
<td>3.1</td>
</tr>
<tr>
<td>TSH decreased &lt; LLN and ≤ LLN at baseline</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

1 The frequency cut off is based on any grade change from baseline
2 Grade according to NCI CTCAE version 4.03

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

Of 2280 patients who received IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent, 69 patients (5%) tested positive for treatment-emergent anti-drug antibodies (ADA) and 12 (0.5%) tested positive for neutralizing antibodies. The development of ADA against durvalumab appears to have no clinically relevant effect on its pharmacokinetics or safety.

Of 201 patients in the CASPIAN study who received IMFINZI 1500 mg every 3 weeks in combination with chemotherapy for four doses followed by IMFINZI 1500 mg every 4 weeks no patients tested positive for treatment-emergent ADA.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk summary
Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full Prescribing Information].

There are no data on the use of IMFINZI in pregnant women.

In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery resulted in an increase in premature delivery, fetal loss, and premature neonatal death (see Data). Human immunoglobulin G1 (IgG1) is known to cross the placental barrier; therefore, durvalumab has the potential to be transferred from the mother to the developing fetus. Aporine 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 2.4% and 15-20%, respectively.

Data
Animal Data
As reported in the literature, the PD-1/PD-1L pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, disruption of PD-1L signaling was shown to result in an increase in fetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature delivery, fetal loss (abortion and stillbirth), and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

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

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

Data
In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature neonatal death.

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

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

Geriatric Use
Of the 478 patients treated with IMFINZI in the PACIFIC study, 45% were 65 years or older; while 7.6% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients. The PACIFIC study did not include sufficient numbers of patients aged 75 years and over to determine whether they respond differently from younger patients.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

PATIENT COUNSELING INFORMATION
Advising patients to read the FDA-approved patient labeling (Medication Guide).

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

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.
- Collitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypophysitis.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs of nephritis.

Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermatological reactions.

Infusion-Related Reactions:
Advising patients to contact their healthcare provider immediately for signs or symptoms of acute anaphylaxis, immune thrombocytopenia, myocarditis, hemolytic anemia, myositis, uveitis, keratitis, and myasthenia gravis.

Infusion-Related Reactions:
Advising patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.2) in the full Prescribing Information].

Complications of Allogeneic HSCT:
Advising patients of potential risk of post-transplant complications [see Warnings and Precautions (5.2) in the full Prescribing Information].

Embryo-Fetal Toxicity:
Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3) in the full Prescribing Information].

Advising females of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI [see Use in Specific Populations (8.3) in the full Prescribing Information].

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

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca UK Limited, 1 Francis Crick Ave., Cambridge, England CB2 0AA
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07/21 US-56258 8/21
**FIGURE.** Adverse Events in the REFLECT Trial

<table>
<thead>
<tr>
<th>AE</th>
<th>Lenvatinib grade 1-2 AEs</th>
<th>Lenvatinib grade 3+ AEs</th>
<th>Sorafenib grade 1-2 AEs</th>
<th>Sorafenib grade 3+ AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Decreased appetite</td>
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<td></td>
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</tr>
<tr>
<td>Decreased weight</td>
<td></td>
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<td></td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Alopecia</td>
<td></td>
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<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Nausea</td>
<td></td>
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<td></td>
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<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Decreased platelet count</td>
<td></td>
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<tr>
<td>Elevated AST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Vomiting</td>
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<td></td>
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<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Increased blood bilirubin</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*AE, adverse events; AST, aspartate aminotransferase.*

**POLLING QUESTION**

What is your comfort level with management of AEs associated with lenvatinib?

- **25%** Very Comfortable
- **75%** Comfortable

**DISCUSSION QUESTION**

What AEs have required management or intervention when treating patients with lenvatinib?

**FINN:** What are your thoughts on the toxicity profiles of lenvatinib and sorafenib [Nexavar]. Does this affect how you use either sorafenib or lenvatinib and manage these toxicity profiles?

**MUSHTAQ:** I used sorafenib a couple years ago. It’s a pretty hard drug, and it’s not easy to use compared with lenvatinib, especially if you’re using a dose of lenvatinib less than 16 mg, like the 12-mg [dose for HCC], which is pretty well tolerated. Mainly the issues [with sorafenib] are diarrhea, which you can manage, and rash, which I have also seen. Looking at efficacy and toxicity, I’ll probably go with lenvatinib, although the overall survival benefit was not statistically significant.

**FINN:** The GI [gastrointestinal] toxicity is not too different between the 2 drugs. However, there’s more hand-foot syndrome with sorafenib and it is higher grade, and there is more hypertension with lenvatinib vs sorafenib. Do you manage these proactively? What is your approach to keeping patients on the drug and managing these AEs? Or do you see some different AEs that you have challenges managing?

**CHEN:** I see more hypertension with lenvatinib, and sometimes, we do need to put people on more hypertensives.
for that. I usually have my patients record their blood pressure. I do see more of an appetite loss or weight loss [with lenvatinib], but I think overall those are able to be managed well. So I tend to use lenvatinib a lot more now than sorafenib.

FINN: How do you manage the weight loss and anorexia? That’s probably the hardest thing for me because there’s no quick fix.

CHEN: [There are] no good ways. Make sure to have them see a nutritionist, make sure they are taking supplements [such as] Ensure and Boost, and use dose modifications.

ZHOU: I have patients [for whom] the problem is the mucositis.

FINN: Yes, some patients do tend to get mucositis. That can be a challenge. There are mucositis [treatments], viscous lidocaine. Sometimes you do need to use a dose reduction. Not the most common AE, but it certainly can be seen.

FARJAMI: I have a couple of cases that have very poorly controlled blood pressure, despite all the efforts and consultants. We ended up switching from lenvatinib to sorafenib. I would say it’s a challenge in some patients, specifically if they have a history of ischemic heart disease or any prior history of a stroke.

FINN: While they are both VEGF receptor inhibitors, lenvatinib is clearly a much more potent compound, and [that] probably explains this difference.

RASILA: I’ve used lenvatinib. The main AE is hypertension. For most patients, it’s manageable. I did have one patient who ended up in the emergency department with a hypertensive

**FIGURE 2. Lenvatinib Dose-Reduction Recommendations**

- **Starting dose**
  - Weight < 60 kg: 8 mg QD
  - Weight ≥ 60 kg: 12 mg QD

- **First dose reduction**
  - Weight < 60 kg: 4 mg QD
  - Weight ≥ 60 kg: 8 mg QD

- **Second dose reduction**
  - Weight < 60 kg: 4 mg Q2D
  - Weight ≥ 60 kg: 4 mg QD

- **Third dose reduction**
  - Weight < 60 kg: Discontinue
  - Weight ≥ 60 kg: 4 mg Q2D

QD, every day; Q2D, every second day.

**Warnings for Prescribing Lenvatinib**

Warnings from the lenvatinib label include hypertension, cardiac dysfunction, arterial thrombotic events, hepatotoxicity, renal failure/impairment, proteinuria, diarrhea, gastrointestinal perforation/fistula, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impaired wound healing, osteonecrosis of jaw, and embryo-fetal toxicity.
emergence, and we did end up discontinuing the lenvatinib. But most of the time, it’s manageable.

FINN: Do you see your patients on lenvatinib on a regular basis? Even though these drugs are oral, I think the patients still need to be seen [regularly] because there are toxicities.

RASILA: Yes, usually anytime I’m starting a new TKI, I will see them 7 to 10 days after. I usually prefer an office visit so I can see if there is any rash, hand-foot-mouth sores, and what their blood pressure is. If they’re doing OK, I’ll [see them] every 2 weeks [initially, and] if they’re fine, then they’ll go to monthly. We are doing more [telemedicine] visits. [Although] for some problem patients, we will still have them do home blood pressure readings. But if there’s something I can’t see on the video, we’ll have them come into the office.

FINN: The one thing we did not touch on specifically is hypothyroidism. TSH [thyrotropin] should be checked intermittently on these patients. It is not uncommon for patients to develop hypothyroidism with lenvatinib.

What are the practical considerations for dosing and management of lenvatinib?

FINN: Typically in liver cancer, patients receive 4-mg lenvatinib tablets, and that’s easy to adjust from 12 mg to 8 mg to 4 mg [Figure 2]. If they start at 8 mg, 8 mg to 4 mg, to 4 mg every other day. Sorafenib is at 200 mg, [which] we’ve been using for a long time with 2 tablets twice a day, [reduced to] 2 tablets once a day, [then to] 2 tablets every other day. There are no specific contraindications on the label for lenvatinib [Warnings for Prescribing Lenvatinib]. Certainly, hypersensitivity could be included there. The boxed warnings are reflective of a class effect, [including] a few more AEs such as proteinuria because it’s a more potent VEGF inhibitor.

### TABLE. Selected Results From the REFLECT Trial

<table>
<thead>
<tr>
<th></th>
<th>LENVATINIB</th>
<th>SORAFENIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median treatment duration</td>
<td>5.7 months</td>
<td>3.7 months</td>
</tr>
<tr>
<td>Dose interruption due to TRAE</td>
<td>40%</td>
<td>32%</td>
</tr>
<tr>
<td>Dose reduction due to TRAE</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>Drug withdrawal due to TRAE</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Second-line therapy received</td>
<td>33%</td>
<td>39%</td>
</tr>
</tbody>
</table>

TRAE, treatment-related adverse event.

**RESULTS OF REFLECT STUDY**

Targeted Oncology™: What were the results of the REFLECT study comparing lenvatinib with sorafenib?

FINN: The REFLECT study [NCT01761266] was the first study in frontline treatment of liver cancer that succeeded in its end point. It was a global study. It took patients who had Child-Pugh A status, it took patients who were Barcelona stage B or C (C is advanced; B is that intermediate group), and it excluded patients that had more than 50% of their liver involved, bile duct invasion, or, importantly, portal vein invasion at the main portal vein. It had standard stratification factors. Lenvatinib [was given at a dose of] 12 mg vs [400-mg twice-daily] sorafenib, and this was an open-label study. Lenvatinib is dosed once daily, and the primary end point is overall survival. REFLECT did exclude patients with main portal vein invasion, [whereas the SHARP trial (NCT00105443) of sorafenib did not].

This study was powered for noninferiority. If lenvatinib was clearly better than sorafenib, that would fine. However, the study was also powered to have enough patients to demonstrate that lenvatinib is potentially noninferior to sorafenib. In a noninferiority study, we say that the upper limit of the hazard ratio can have some cutoff. If it’s less than 1.0, it would be superior. But if it’s greater than 1.0, if it was between 1.0 and 1.08, we would call that noninferiority.

The primary end point of overall survival for sorafenib was 12.3 months and for lenvatinib was 13.6 months. And the hazard ratio is 0.92, but the upper limit of that confidence interval was 1.06. So that 1.06 is less than the prespecified 1.08. Therefore, this study met its end point of being noninferior, and this was the basis for the FDA approval.

Now, interestingly, while it did not statistically improve overall survival, it did significantly improve progression-free survival as well as time to progression. For the first time, we had a drug that induced a significant number of partial responses. The objective response rate (ORR) of 24% is using the modified RECIST criteria. This takes into account not just the total sum of the tumor diameter, but also...some of the enhancing components. But even by conventional RECIST, the ORR was around 19%.

The median duration of treatment was longer with lenvatinib [Table]. Discontinuation rates were slightly higher, but again, patients were on treatment longer. In second-line therapy received, you can see there was an imbalance. Interestingly, despite the [adverse event] differences, lenvatinib did delay deterioration in quality of life for several specific items, such as role function, diarrhea, pain, body image, nutrition, fatigue, and sexual function, compared with sorafenib.

This was a nice data set in that even though it was noninferior for its [overall survival] end point, many of the secondary end points support its use.
Targeted Oncology™: What data support the use of polatuzumab vedotin in transplant-ineligible patients with relapsed or refractory DLBCL in the second-line setting?

**MUNOZ:** We have established that patients with transplant-ineligible relapsed or refractory DLBCL fare poorly with standard chemotherapy, as they usually have an ominous prognosis. The antibody-drug conjugate [ADC], polatuzumab vedotin [Polivy], is a novel agent that targets CD79b, a B-cell receptor component. The phase 2 study of POLA-BR [polatuzumab plus bendamustine (Treanda) and rituximab (Rituxan)] included transplant-ineligible patients or those with treatment failure with prior ASCT [autologous stem cell transplant] who were [randomly assigned] to get either POLA-BR or BR.

It is a 21-day cycle treatment for 6 cycles, and the dose doesn’t go up or down unless there’s toxicity. If there is neuropathy, then one can tweak the dose. But if the patient does well, it is a flat dose of 1.8 mg/kg of polatuzumab [intravenously], 90 mg/m² of bendamustine, [and 375 mg/m² of rituximab], as many of us prescribe.

This POLA-BR study [NCT02257567] led to an accelerated approval of POLA-BR in 2019. More than 80% of patients had advanced-stage DLBCL. The median prior lines of therapy were 2, but some patients had received up to 7 prior therapies. Seventy-five percent to 85% of patients were refractory to the last prior therapy.

Anyone who has treated someone with an aggressive lymphoma refractory to the last therapy knows one is in a hurry because of being a little bit against the ropes. For the POLA-BR, the overall response rate [ORR] was approximately 45%, primarily driven by complete responses [CRs], which was attractive.

With so many bad actors for a treatment that you give every 3 weeks, it is reasonable to have an ORR of more than 40% that is mainly driven by CRs. One can have high response, but if it’s only going to put you in remission for 1 month, then it’s just not worth your effort.
You need to get some months, so maybe you could pivot on this treatment and do something else, whether it is CAR [chimeric antigen receptor] T-cell therapy or transplant, if the patient is a candidate for that. With that, I was thinking allogeneic SCT, because by now you are thinking of third-line therapy. The duration of response [DOR] is not a panacea [or] a home run, but it does help a lot of patients, particularly with the over 40% ORR [Figure 3]. And there is 9 to 10 months DOR in these patients.

Could this treatment be a bridge to transplant or CAR T-cell therapy?

Perhaps. I must admit I do use it pre-CAR T-cell therapy, but I deviate from the label, so I navigate with caution when it comes to my comments. Obviously, follow the FDA label and the National Comprehensive Cancer Network guidelines.

I must also admit I prescribe it without bendamustine because I’m afraid of the effects of chemotherapy on T cells. Bendamustine is lymphotoxic. In the ZUMA-2 study [NCT02601313] that used CAR T-cell therapy in mantle cell lymphoma, patients who got bendamustine before CAR T-cell therapy did a little worse than those who did not. I think that is interesting and because of that, I have a bias extrapolating. Of course, take this with a grain of salt. I’ve been doing some POLA-R instead of POLA-BR, but POLA-BR [is approved].

The overall survival [OS] was better for [patients on] POLA-BR compared with BR, at approximately 12 months vs 5 months, which is a big difference. Now, would you go just with BR in a patient with relapsed or refractory DLBCL? You can, but the responses are not going to be as good, and they’re not going to last like that of POLA-BR.

Remember that ADCs have a small amount of chemotherapy. In this case, vedotin monomethyl auristatin E [MMAE]. It is internalized once the linker with the antibody is cleaved, so the payload is delivered in a smart fashion. Vedotin [MMAE] is a tubulin antimitotic agent reminiscent of vincristine [Oncovin], which can cause neuropathy. Not surprisingly, POLA-BR has more peripheral neuropathy than BR. Of note, grade 3 or 4 toxicity is 0% in both arms, which is reassuring. That means the disabling neuropathy is not there, but the garden variety neuropathy does

![Figure: Phase 2 Study of Polatuzumab Vedotin Plus BR Objective Response](chart)

**FIGURE.** Phase 2 Study of Polatuzumab Vedotin Plus BR Objective Response

* Does not include missing or not evaluable patient data.

BR, bendamustine and rituximab; CR, complete response; IRC, independent review committee; OR, objective response; PD, partial disease; PR, partial response; POLA-BR, polatuzumab vedotin plus bendamustine and rituximab; SD, stable disease.

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* Does not include missing or not evaluable patient data.

BR, bendamustine and rituximab; CR, complete response; IRC, independent review committee; OR, objective response; PD, partial disease; PR, partial response; POLA-BR, polatuzumab vedotin plus bendamustine and rituximab; SD, stable disease.
appears with POLA-BR. One [must] keep an eye on it and [ensure] it is not getting worse.

**POLING QUESTION**

At a live virtual event, Munoz asked participants, “What would you most likely recommend for this patient now, after chemoimmunotherapy?”

- Tafasitamab and lenalidomide 50% (4)
- Polatuzumab vedotin BR 25% (2)
- Loncastuximab tesirine 12% (1)
- Other/clinical trial 12% (1)
- Rituximab-based chemotherapy 0% (0)

Total votes: 8

What treatments do you consider for patients with newly diagnosed DLBCL compared with further lines of treatment?

We have plenty of newly diagnosed patients with DLBCL to go around. It’s the most common aggressive lymphoma. But as we go along in the journey—second line, third line, fourth line, fifth line, and so on—patients get fewer, which means our chances of trying all the drugs in multiple patients is going to get smaller. So it makes sense that in some of these agents, we may have less personal experience than in others.

Tafasitamab [Monjuvi] is a naked antibody against CD19. It is not an ADC, so it is different from polatuzumab. Lenalidomide [Revlimid] is an immunomodulator. We honestly do not understand it well. I’ve seen slides trying to explain how lenalidomide works, and they tell you 10 different mechanisms of action. To me, that just means we don’t understand why or how lenalidomide works.

It is approved for the treatment of [patients with] mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma. Polatuzumab was approved in 2019, and tafasitamab and lenalidomide got accelerated FDA approval 1 year later. The approval included DLBCL arising from low-grade lymphoma and patients who were not eligible for ASCT.²

**What data support the use of tafasitamab plus lenalidomide in transplant-ineligible patients with relapsed or refractory DLBCL in the second-line setting?**

The phase 2 trial for tafasitamab plus lenalidomide had the catchy name, L-MIND [NCT02399085], and the primary end point was ORR. Patients included were those with relapsed or refractory DLBCL who had 1 to 3 prior therapies and were transplant ineligible. Primary refractory patients were excluded.

The induction from cycle 1 to 3 is more intense. It gets better from cycle 4 to 12—we’re still prescribing the doublet but not as often for tafasitamab. Finally, you have maintenance tafasitamab after cycle 12, without lenalidomide until progression of disease.³ POLA-BR is just a little easier, [as] it is given every 3 weeks. If you are having no severe adverse effects [AEs], it’s just a flat dose, but it doesn’t mean this is a bad combination by any means. It’s just a little different than how we dose POLA-BR.

The median line of previous therapy was 2 but up to 4. It was mainly 1 or 2 prior therapies, which were 50% and 43% of patients, respectively. There were also 44% of patients who were refractory to prior therapy and 11% of patients with prior ASCT,⁵,⁶ so some bad actors there for sure. The primary end point, which was ORR, was 57.5%, [which] is encouraging. And from that, 40% were CRs, like with POLA-BR, and the median DOR was 43.9 months, which is quite impressive.⁵,⁶

The median progression-free survival [PFS] was 11.6 months, so almost 1 year. The median OS was 33.5 months, so almost 3 years.⁶ Again, I understand why several of our colleagues chose tafasitamab plus lenalidomide. It has a good ORR, PFS, and OS. It is a treatment you can prescribe, and it is not available only in boutique centers.

Now, trying to be the devil’s advocate, I always have some pause outside of a randomized trial to compare a trial that has a finite duration of therapy. POLA-BR—6 cycles and you’re done—compared with a regimen that has some sort of maintenance plugged into it, particularly with drugs that have activity like tafasitamab, which you keep pushing for weeks, months, and so on.

Some of these trials are designed until progression of disease, and if the drug you continue to prescribe is active, you will assume that duration could be a little more handsome than the ones that have a finite duration of therapy. That is something to consider. The trial designs were different, so it’s not necessarily apples to apples.

**What AEs should be highlighted with this treatment?**

For polatuzumab, it was neuropathy. For tafasitamab plus lenalidomide, the toxicity is mainly hematologic. Regarding grade 3 or 4 toxicity, the No. 1 toxicity was neutropenia, No. 2 was thrombocytopenia, [and] No. 3 was anemia and leukopenia. There were no grade 5 events. Grade 4 toxicities are single digits, except neutropenia, which is something expected in the relapsed or refractory setting.

To me, beyond the neutropenia, what matters the most is febrile neutropenia. [Although] 21% of patients had grade 4 neutropenia, only 2% of patients had grade 4 febrile neutropenia.⁵,⁷ So between those 2, I would go by...
the febrile neutropenia as a more actionable and more relevant variable. Regarding nonhematologic toxicities, there were no grade 5 events. Grade 3 to 4 toxicities were single digits. Numerically, the highest grade 3 toxicity was rash, [which is] somewhat expected in a regimen that uses lenalidomide [and] something I have seen, even in single-agent lenalidomide.

If toxicity is low, then discontinuation should be low, too. Only 12% of patients discontinued [because of] toxicity. Of course, you have some other variables there, [such as] serious AEs, AEs of special interest, or treatment-emergent AEs [that] lead to death, which was up to 13%. Remember some of these patients are preordained to have an outcome, and death is going to happen with or without these agents. Not surprisingly, lenalidomide has a large contribution regarding toxicity.

What data support the use of loncastuximab tesirine in transplant-ineligible patients with relapsed or refractory DLBCL in the third-line setting?
The debate was between POLA-BR and TAFA-LEN [tafasitamab plus lenalidomide]. They are available as second-line therapy. Loncastuximab [tesirine; Zynlonta] is available as third-line therapy. Maybe that is why as we go along, we start seeing less and less patients through this journey. It makes sense that the numbers are lower when it comes to our own experience with loncastuximab [tesirine].

The catchy name for the loncastuximab tesirine [LONCA-T] trial is LOTIS-2 [NCT03589469]. If you notice the accelerated approvals, POLA-BR received it in 2019, TAFA-LEN in 2020, and LONCA-T in 2021.8

So there was that beautiful crescendo 1 year after another as these 3 agents got their accelerated approvals. LONCA-T is another ADC; [however], the payload is not MMAE but an agent called pyrrolobenzodiazepine.7 They call it a warhead, but [because of] the current bellicose international landscape, I’m going to say payload instead. Reminiscent of the previous study, there is a more intense induction, but it becomes easier for patients as we go along. Every 3 weeks, [patients] get a higher dose for 2 cycles, then a lower dose for 2 cycles, and then the dose is maintained every 12 weeks for up to 3 years.10 It is easier, better, [and] more patient friendly.

They had some bad actors, including double-hit lymphoma [and] prior CAR T-cell therapy failure, each [approximately] 10%. The median prior therapies was 3, so patients were slightly more heavily pretreated with LONCA-T than the other 2 agents.10

The CR is 24% and PR [partial response] is 24%, making an ORR of 48%.10 The CR may be a little lower than those of the other 2 agents, but remember, these patients were more heavily pretreated, so it’s a little unfair to try to compare just the numbers and say one is better than the other. The median DOR seems to be [approximately] 1 year in general, but for the patients who achieved CR—at least based on the last update—the median DOR had not been reached, which is important.10

If you’re among those 24% of patients who achieve CR, maybe you could have a long DOR, so don’t rule it out. Keep it on the table as a tool in your tool belt because there is a role for this medication.

This trial permitted transplant-eligible and transplant-ineligible patients. It had data for transformed DLBCL and double-hit lymphoma. This is included in the FDA indication, [which] makes it a bit unique. The ORR data for patients who did and did not receive prior CAR T-cell therapy seem similar, but of course, this was a small number of patients.10

How would you sequence these therapies?
These are the questions that keep me up at night, particularly sequencing of the anti-CD19 agents. We have anti-CD19 CAR T cells, anti-CD19 monoclonal antibodies,
[and] anti-CD19 ADCs. Does sequencing matter? It is CD20 agents [like] rituximab that we keep hammering down through multiple lines of therapy, but it mostly does not seem to be an issue with CD20. We just keep recycling rituximab and patients usually do well, maybe because of the agent you’re combining rituximab with but rituximab probably has something to do with it, too.

Now remember, when you have a hammer, everything looks like a nail, and now we have the anti-CD19 hammer that is proving to be quite rewarding in these trials. Fourteen patients received CAR T cells after LONCA-T, they had an ORR of 46%, and fast responses were 1.4 months. It seems like not all is lost after you fail CAR T cells. Remember, CAR T cells’ FDA approvals occurred during this LONCA-T trial, [which] is why you started seeing some [patients with] CAR T-cell failure join the study. Sadly, cancer keeps giving us second chances to try other drugs.

Bad actors also respond; of 11 patients with high-grade B-cell lymphoma [HGBCL], 5 had CR, [which] gave LONCA-T the label for double-hit lymphoma. It’s amazing. It is such a bad disease that if you see a signal with 5 patients going into CR, you get an approval on your label. Interestingly, it may take a little longer to achieve that response in patients with HGBCL—79 days, to be exact, vs 43 days for the garden variety DLBCL.

The best responses to LONCA-T after CAR T cells was a CR of 15% and PR of 30%. It’s not a home run, but there are responses. The critics will point out the small numbers and short follow-up. They’re probably right, but there seems to be a signal there, and it’s a good weapon to have in the armamentarium.

For toxicity of LONCA-T, there is myelosuppression and peripheral edema, so keep an eye on those. The trial tested for GGT [gamma-glutamyl transferase]. I’m not sure how many of you test for GGT in the clinic, but if you ask the question, sometimes you will get an answer. What they saw in the trial is that GGT was increased. In my eyes, you also see the alkaline phosphatase and alanine transaminase are not dramatically increased, but alanine transaminase are not dramatically increased, but the aspartate aminotransferase and GGT. Usually, the aspartate aminotransferase and alanine transaminase are not dramatically increased, but the peripheral edema is real, and patients can have weight gain and pleural effusions. It’s not only lower-extremity edema, so you need to pull the trigger there relatively quickly with diuretics. This trial encouraged the use of spironolactone [Aldactone].

Comparison is truly the thief of joy, but it is so tempting to compare. Again, proceed with caution. These were not randomized trials. Remember [that] some were more complex than others. In the L-MIND trial, one could prescribe the agent until progression of disease. In LOTIS-2, it was 1 year, and POLA-BR was 6 cycles. POLA-BR was for the transplant-ineligible patients or those with treatment failure with prior ASCT. L-MIND was for the transplant-ineligible [patients], too. LOTIS-2 permitted those who received ASCT 30 days prior or allogeneic SCT 60 days prior. Also, the primary end points were different; it was CR for POLA-BR [and] ORR for TAFA-LEN and LONCA-T.

REFERENCES
**Roundtable Discussion:**

**Sequencing and Tolerability Sway Treatment Choices for Patients With Clear Cell RCC**

**CASE SUMMARY**

A 59-year-old Black woman received a diagnosis of clear cell renal cell carcinoma (RCC). She underwent left total nephrectomy in December 2019. Nine months later, she developed metastatic disease to bilateral lungs, mediastinum (35 × 38 mm), and retroperitoneal lymph nodes. She received a diagnosis of stage IV RCC, clear cell histology, with metastases in the lungs and retroperitoneum. Her Karnofsky performance status score was 90%. Her hemoglobin was 11.1 g/dL, but corrected calcium, neutrophils, and platelet levels were within normal limits.

**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:** With a diagnosis of recurrent metastatic clear cell RCC, how do you assess risk? Is there a tool that you use?

**SUMOZA:** [We look] into the risk models and based on that, we decide what to use.

**KUZEL:** Do you find one easier to use than the other or have preferences?

**SUMOZA:** Probably the Memorial Sloan Kettering Cancer Center risk model; it...has been [around] for a longer period of time in the guidelines.¹

**KUZEL:** It also has 1 fewer point to remember. The IMDC [International Metastatic RCC Disease Consortium] risk calculator is another alternative.²

The Memorial Sloan Kettering criteria was the first of the risk-scoring models and was used in a large number of clinical trials to stratify patients...Basically the tools are designed to identify favorable-risk, intermediate-risk, and poor-risk patients. Some of our therapies are approved for 1 setting or another, so this becomes a valuable tool.

The IMDC is a web-based tool. It takes some of the memory and the thinking out of it. You can pop up the web-based tool, click in the patient's clinical features, and it will then automatically calculate the number of features and give you the risk stratification.

In this case, based on this patient’s features—rapid recurrence risk, good performance status, mild anemia, and all other normal laboratory parameters—she has 2 risk factors, and she would be intermediate risk. We will move forward and think about what that implies for treatment here.

continued on page 101
ENGINEERED FOR A CHALLENGING LANDSCAPE

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

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

Interstitial Lung Disease/Pneumonitis

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

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

Dermatologic Adverse Reactions

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

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

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

**ORR**

- 40% (95% CI: 29%, 51% (n=81))
- 3.7% of patients achieved a CR
- 36% of patients achieved a PR
- Efficacy was evaluated by ORR and DOR

**MEDIAN DOR WAS 11.1 MONTHS**

(95% CI: 6.9, NE)

**The safety of RYBREVANT® was evaluated in the CHRYSLIS® study (n=129)**:
- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%)
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%)
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion
- Based on the safety population, N=302.

The innovation you’ve been waiting for. | RYBREVANThcp.com

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist.

Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

**Ocular Toxicity**

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.5% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist.

Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

**Embryo-Fetal Toxicity**

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

**Adverse Reactions**

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%).

Adverse reactions (≥20%) also included: rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%).

**References**

RYBREVANT™ (amivantamab-vmjw) injection

occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions [see Warnings and Precautions]
- Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions]
- Dermatologic Adverse Reactions [see Warnings and Precautions]
- Ocular Toxicity [see Warnings and Precautions]

Clinical Trials Experience

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

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 242 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients ≤80 kg) or 1400 mg (for patients >80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphorus, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

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

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

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

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

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

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

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

Clinical Adverse Reactions

   - Infusion-Related Reactions

   - Intestinal Lung Disease/Pneumonitis

   - Dermatologic Adverse Reactions

   - Ocular Toxicity

INDICATIONS AND USAGE

RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in Full Prescribing Information], whose disease has progressed on or after platinum-based chemotherapy.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

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

Intestinal Lung Disease/Pneumonitis

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

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

Dermatologic Adverse Reactions

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

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

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

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

Ocular Toxicity

RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population [see Adverse Reactions], keratitis
Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVANT (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash²</td>
<td>84</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
</tr>
<tr>
<td>Fatigue³</td>
<td>33</td>
</tr>
<tr>
<td>Edema⁴</td>
<td>27</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
</tr>
<tr>
<td>Pneumonia⁵</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain⁶</td>
<td>47</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea¹</td>
<td>37</td>
</tr>
<tr>
<td>Cough⁷</td>
<td>25</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Stomatitis⁸</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain¹</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage¹</td>
<td>19</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy⁹</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Headache¹</td>
<td>10</td>
</tr>
</tbody>
</table>

¹ Rash: acne, dermatitis, dermatitis aciform, eczema, eczema atopic, palmar-planter erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash papulosus, skin exfoliation, toxic epidermal necrosis
² Fatigue: asthenia, fatigue
³ Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
⁴ Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
⁵ Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
⁶ Dyspnea: dyspnea, dyspnea exertional
⁷ Cough: cough, productive cough, upper airway cough syndrome
⁸ Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
⁹ Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
¹⁰ Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
¹¹ Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
¹² Headache: headache, migraine

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

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

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

¹ The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

Immunogenicity

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

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

**Pregnancy Testing**

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

**Contraception**

**Females**

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

**Pediatric Use**

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

**Geriatric Use**

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

**PATIENT COUNSELING INFORMATION**

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

**Infusion-Related Reactions**

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

**Interstitial Lung Disease/Pneumonitis**

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

**Dermatologic Adverse Reactions**

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

**Ocular Toxicity**

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

**Paronychia**

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

**Embryo-Fetal Toxicity**

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

**Lactation**

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

**Product of Ireland**

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864

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**POLLING QUESTION**

“A decision was made to initiate systemic therapy. What frontline therapy are you most likely to choose for this patient?”

- Axitinib/pembrolizumab 63% (5)
- Nivolumab/ipilimumab 25% (2)
- Lenvatinib/pembrolizumab 12% (1)
- Cabozantinib/nivolumab 0% (0)
- Cabozantinib 0% (0)
- Other 0% (0)

Total votes: 8

**KUZEL:** For those of you who chose axitinib [Inlyta]/pembrolizumab [Keytruda], is there any particular reason why that was your choice?

**MULHERIN:** I think it is fairly well tolerated. [Also,] the patient is 59 years old and she is in relatively good shape. I am anticipating she is probably going to survive into the second-line setting as many of these patients do, so I also think about planning out a sequence for what would I like to use next. I like to use cabozantinib [Cabometyx] as second-line therapy if they did not get it in the frontline setting. I probably tend to use nivolumab [Opdivo]/cabozantinib in patients who are frail; I think it is a bit easier. By comparison, I found lenvatinib [Lenvima] to be probably the most difficult TKI [tyrosine kinase inhibitor] of the 3 out there. So although I have used that, I have used it in the most symptomatic patients. You can look at the data and try to do cross-trial comparisons and all that, but that is just my experience.

**KUZEL:** For those who chose ipilimumab [Yervoy]/nivolumab, what is your rationale?

**STANKIEWICZ:** I chose nivolumab/ipilimumab because it can be time-limited therapy if she responds well. After ipilimumab is done, you can continue nivolumab, and if she is doing well at 2 years, maybe she can stop.

**KUZEL:** If you chose a combination with a TKI, do you continue it past 2 years if the patient is doing well?

**STANKIEWICZ:** I do not. It depends how they tolerate it. Sometimes you can drop the TKI even sooner and continue with the immunotherapy only.

**CASE UPDATE**

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

**DISCUSSION QUESTIONS**

- What is your impression of the safety/tolerability of lenvatinib/pembrolizumab?
- Are you familiar with the recommended dosages for this regimen?
- Do you have experience using lenvatinib in RCC with everolimus (Afinitor)?

**KUZEL:** [Has anyone] used lenvatinib/pembrolizumab? Often I find when I speak to community-based doctors, their exposure to lenvatinib tends to be more [with] thyroid cancer, or lenvatinib/pembrolizumab in other cancers. What is your expectation of toxicity?

**CONTE:** Yes, that sounds about right. It is not an easy medication. I heard from speakers in the gynecologic oncology world that they do not start at the full dose anymore. They now go in with 14 mg as the starting dose. Everybody has their own preference.

**KUZEL:** They have given up on the 20 mg altogether. That is interesting.

**CONTE:** One well-known speaker said that. Another speaker contradicted it.

**KUZEL:** Yes, that is a debate that you often will see. Is it better to start with a full dose and then have toxicity and dose reduce? Or is it better to start at a lower dose and then stay there? Unfortunately, there aren’t trials that answer those questions, so it becomes treator-dependent, and up to your philosophy.

There is no doubt with lenvatinib, hypertension in particular can be a significant adverse event [AE]. Have you used lenvatinib at 20 mg in thyroid cancer? Do you find 20 mg is tolerable there?

**MULHERIN:** When I have used it in thyroid cancer, almost all of the patients have been younger. I have used 20 mg, but I had to dose reduce a fair number of those—not everyone. It is not the hypertension; we can usually deal with hypertension. I find it causes more fatigue, stomatitis, nausea, and anorexia. I think it is those vaguer things that tend to be more problematic.

**MULHERIN:** When I have used it in RCC, almost all of the patients have been younger. I have used 20 mg, but I had to dose reduce a fair number of those—not everyone. It is not the hypertension; we can usually deal with hypertension. I find it causes more fatigue, stomatitis, nausea, and anorexia. I think it is those vaguer things that tend to be more problematic.

**CONTE:** How do you feel about everolimus in RCC? It is interesting.

**KUZEL:** When you start with everolimus in RCC, what is your starting dose? A lot of clinicians start at 15 mg, but do you prefer a lower dose, or do you start at the full dose, and then reduce? It is interesting.
MULHERIN: After cabozantinib, but it’s hard.

KUZEL: What do you do after cabozantinib, [if] they are in the second line?

MULHERIN: If they start with nivolumab/cabozantinib, you might consider doing something [with lenvatinib] as second line. They are never going to be as fit as in the frontline setting. You want to use your most-effective regimen upfront.

How likely is it that they are going to survive at second-line setting? The poor-risk patients, maybe not so much; an unhealthy minority will not. In the favorable and intermediate risk, it tends to be higher. So if I do nivolumab/cabozantinib upfront, it tends to be in the frailer patients. But then I [use a lenvatinib combination] as second line and it is harder, and I probably dose reduce most of those patients to start with.

KUZEL: Is your choice of pembrolizumab/axitinib somewhat familiarity driven? It was the first combination [available].

MULHERIN: Sure, first-mover advantage.

KUZEL: You all learned to use it, so you keep using it to some extent. Overall, second-line therapy does drive your first-line choice, as well as just familiarity with these drugs.

**DISCUSSION QUESTIONS**

- What do you think of the nivolumab/cabozantinib combination, as used in CheckMate 9ER (NCT03141177)?
- What is your impression of the safety/tolerability of this regimen?
- Are you familiar with the recommended dosages?

KUZEL: The overall survival data in this trial were updated [HR, 0.70; 95% CI, 0.55-0.90]. Does it change the way you think about this regimen? At 2 years, 70% of patients were still alive. Is this a regimen that can make you think twice about ipilimumab/nivolumab or pembrolizumab/axitinib?

SHADE: My impression is that compared with pembrolizumab/axitinib, it is similar in terms of efficacy, but a little bit more toxic.

STANKIEWICZ: Especially for certain patients, the TKIs are quite difficult to take, and to continue to take. This is my impression. They have a quite a few AEs and patient adherence may be at question. Patients do not like feeling tired or having diarrhea and mucositis. All this is manageable, so it depends how patients are truly dealing with it—if they have support or not—but they are not easy to take. I know there are advantages of getting a better response rate, or hopefully this is going to translate into overall survival; but [CheckMate 9ER regimen] compared with sunitinib [Sutent] does not seem like it is a huge advantage in overall survival. It’s a few months.

SUMOZA: Tolerability and toxicity, we have to consider all this. Sometimes it is hard for some patients to tolerate this treatment.

KUZEL: Are you an ipilimumab/nivolumab fan, or pembrolizumab/axitinib?

SUMOZA: I am an ipilimumab/nivolumab fan.

KUZEL: Fair enough, avoiding the TKI if you can for a while. The dosing in the CheckMate 9ER trial: It’s important to remember that cabozantinib is only 40 mg in the combination arms. I think some [clinicians] remember 60 mg of cabozantinib as being a bit harsh, which is the single-agent dose, but it is only 40 mg in this combination. For those of you who have used this combination, do you think that makes it much easier? Or is it still a bit of a challenge?

CONTE: I think any dose reduction helps. In rural practices, where we have a lot of [older] patients in their 70s and 80s, they have a lot of AEs. They get upset; they will refuse to come back to the clinic. They will refuse anything if it is too difficult in the beginning. You have to talk them into treatment and then if they have all these AEs, they feel like you have betrayed them. I remember 10 years ago when we had none of these medications, we had many patients on single-agent pazopanib [Votrient], any age group, and many had very few AEs. Some had a good response. So I think in [older] patients, especially with good prognostic features, single agent is a possibility too.

SHADE: I agree with that…[For] the [older] patients, a lot of times I might start with a single-agent TKI and reserve checkpoint inhibitor for next line.

KUZEL: What is your preferred single-agent TKI?

SHADE: Pazopanib. For an older, favorable-risk patient, I feel like it is worth a shot. If they do not respond or do not tolerate it, then I have no problem switching; but I think it has a role for favorable [older] patients.
The dosing in the CheckMate 9ER trial: It’s important to remember that cabozantinib is only 40 mg in the combination arms. I think some [clinicians] remember 60 mg of cabozantinib as being a bit harsh, which is the single-agent dose, but it is only 40 mg in this combination.”

—TIMOTHY M. KUZEL, MD

KUZEL: I agree. I think there is a role. Observation, for a favorable older patient, may be the best choice.

DISCUSSION QUESTIONS

• How do you mitigate, monitor, and manage toxicities associated with ICI (immune checkpoint inhibitor)-TKI combination therapy?
• How do you decide which drug to modify when using a combination regimen?
• How often have you had to discontinue all systemic therapy for a patient because of adverse events (AEs)? Immune-related AEs?

KUZEL: Do you do your own toxicity management? Do you have dedicated nurse practitioners or physicians assistants who get all those phone calls?

SIDDIQUI: I think it is a bit of both; myself and my nurse practitioner.

KUZEL: OK, so it is a combination. If [patients] develop autoimmune toxicities with the combinations, do you stop everything? Do you stop just the ICI, ipilimumab, nivolumab, both? Or do you have more issues with the TKIs?

CONTE: If somebody has diarrhea, it is hard to say. Is it the TKI or is it the pembrolizumab? There are some tricks of the trade; I guess one always assumes it is the TKI, but you do not want to miss colitis. So it’s a little tricky.

KUZEL: If you stop both and they get better, do you restart the ICI ever, and say, “We’ll keep our fingers crossed,” or you are done with both?

CONTE: No, I will try to go in with one, and then go in with the other one.

KUZEL: These have been around long enough that I think [clinicians] feel pretty comfortable with those kinds of strategies at this point, fortunately.

Financial toxicity—does anybody have absolutely no luck whatsoever in trying to access any of these drugs for patients? Or [do you] manage to get it?

MULHERIN: It can take a little while, sometimes, to get through the system, but we usually can figure a way. We find a way.

KUZEL: I know some of these come with a 2-week starter pack. Anybody use those, or by the time everything gets going it is 2 weeks anyway? I think lenvatinib has a dose-exchange program. So if you start one and you need to replace a dose, the patient is not stuck with 30 days of 20-mg tablets or something, which is nice. Has anybody used any of those? Or do you just do what it takes [to get the therapy]?

MULHERIN: Yes, but again it usually takes a couple of weeks, anyway, to get through insurance.

REFERENCES

Roundtable Discussion: Panelists Debate Therapy Options for R/R Multiple Myeloma With Renal Impairment

CASE SUMMARY

A 70-year-old White woman received a diagnosis of stage I multiple myeloma. She had a medical history of stage 3 chronic kidney disease with moderate renal impairment. Fluorescence in situ hybridization showed 17p deletion (del17p). The patient declined autologous stem cell transplant. She received VRd (lenalidomide [Revlimid], bortezomib [Velcade], and dexamethasone) with a best response of very good partial response (VGPR). She continued on lenalidomide maintenance.

<table>
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<th>Test</th>
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<td>Skeletal survey</td>
<td>L4-L5 compression fractures</td>
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DISCUSSION QUESTIONS

- How often are you using a quadruplet regimen as first-line therapy?
- What about second-line use of triplet therapy?
- What precautions would you take to protect this patient’s kidney function?

USMANI: This patient [started treatment in 2019]; now we are in 2022, and our perceptions about the data have changed. How many of you are using quadruplet regimens as part of the treatment?

STEINBERG: I would say over the past year or so I’m starting to use quadruplets, maybe in the past 8 to 10 months.

ROTKOWITZ: I think the data from trials like GRIFFIN [NCT02874742]1,2 and CASSIOPEIA [NCT02541383]3 are very impressive, but the difficulty in the community is, I’ll reach out to local and regional thought leaders, and everybody tells me something different. Someone will say, “I’m always using quadruplets,” someone will say, “I’m... continued on page 111
MONJUVI®
tafasitamab-cxix | 200mg
for injection, for intravenous use

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

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

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

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend tafasitamab-cxix (MONJUVI)
in combination with lenalidomide as a second-line or subsequent therapy option for DLBCL in patients who are not candidates for transplant.²*

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

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

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

IMPORTANT SAFETY INFORMATION

Contraindications
None.

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

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.
**MONJUVI**

*tafasitamab-cxix* | 200mg

for injection, for intravenous use

**SECURE RESPONSE IN SECOND LINE**

*MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant*^4^

**INDICATIONS & USAGE**

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

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

**L-MIND study design**^1^

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

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions (cont’d)**

**Myelosuppression**

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

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

**Infections**

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

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

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

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.
1-YEAR PRIMARY ANALYSIS

HIGH ORR REACHED, with a majority of responders achieving CR
1-year primary analysis in patients with R/R DLBCL (N=71)

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

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

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

3-YEAR FOLLOW-UP ANALYSIS

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

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

2Assessed by an Independent Review Committee.1,3

3Kaplan-Meier estimates.1,3

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

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

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

1-3-year follow-up analysis in patients with R/R DLBCL (N=71)

ORR (3-year analysis)

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

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

Patients who had received 1 prior therapy

43% CR
20% PR

Patients who had received 2 or more prior therapies

63% ORR (n=22; 95% CI: 45%, 79%)
28% CR
17% PR

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

Median DoR (3-year analysis)

Median DoR: 43.9 months (95% CI: 15.0, NR)
REACH FOR MONJUVI

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

INDICATIONS & USAGE

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

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IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

To learn more, visit MonjuviHCP.com

For information about patient assistance, visit MyMISSIONSupport.com

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

### INDICATIONS AND USAGE

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

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

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

#### Infusion-Related Reactions

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

#### Myelosuppression

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

#### Infections

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

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

#### Embryo-Fetal Toxicity

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

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

### ADVERSE REACTIONS

#### Clinical Trials Experience

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Title</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue+</td>
<td>38</td>
<td>3.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain+</td>
<td>15</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection+</td>
<td>24</td>
<td>4.9</td>
</tr>
<tr>
<td>Urinary tract infection+</td>
<td>17</td>
<td>4.9</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black pain</td>
<td>19</td>
<td>2.5</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash+</td>
<td>15</td>
<td>2.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Fatigue includes asthenia and fatigue.
*Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection
*Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal
*Abdominal pain includes abdominal pain, abdominal pain lower, and abdominal pain upper
*Rash includes rash, rash maculopapular, rash pruritic, rash erythematous, rash pustular

Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:
- **Blood and lymphatic system disorders**: lymphopenia (6%)
- **Musculoskeletal and connective tissue disorders**: arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- **Neoplasms benign, malignant and unspecified: basal cell carcinoma (1.2%)
- **Nervous system disorders**: headache (9%), paresthesia (7%), dysequesa (6%)
- **Respiratory, thoracic and mediastinal disorders**: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- **Skin and subcutaneous tissue disorders**: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)
MONJUVI® (tafasitamab-cxix)

Table 4 summarizes the laboratory abnormalities in L-MIND.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>MONJUVI1 All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>1.4</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>1.4</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time increased</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

1The denominator used to calculate the rate was 74 based on the number of patients with a baseline value and at least one post-treatment value.

Immunogenicity

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

Refer to the lenalidomide prescribing information for recommendations.

Pediatric Use

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

Geriatric Use

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

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full Prescribing Information.

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never using quadruplets,” and I think there may be an additive fashion, where I’ll use VRd and see them not responding and then add in the anti-CD38 agent. For some patients who I think are high risk up front, I feel that the quadruplet makes a lot of sense.

[For second-line therapy], I’m using triplets across the board. I think everyone is triple-class refractory by third line. But when I move into the second line, if they [previously received] VRd, I’m probably using DRd [daratumumab (Darzalex), lenalidomide, and dexamethasone], DVd [daratumumab, bortezomib, and dexamethasone], or KPd [carfilzomib (Kyprolis), pomalidomide (Pomalyst), and dexamethasone] depending on what they got up front. I’m definitely using a triplet or a quadruplet in the first line and definitely a triplet in the second line.

STEINBERG: I’d say there’s no right and no wrong, but a former colleague of mine told me, “Why would we want to leave our best ammunition unused?” We might as well try to use [quadruplet] in the beginning and give it the best shot to start with. That’s when I’m philosophical. I thought it might be a good idea to try it, and I have been for the past several months. I’ve got to worry about toxicity, but it’s been manageable.

USMANI: There has been a lot of discussion around the quadruplet use in the front line, and one point that we try to make in these forums is we’re not using quadruplets forever. It’s for 4 to 6 cycles, then patients go on to their transplants and maintenance. And if they’re relapsing 2, 3, or 4 years later, there’s no reason why you can’t use the bortezomib or the daratumumab with something that they haven’t seen before. It’s all about trying to get deep responses in that first year of diagnosis. Dr Rotkowitz raised an important point about the high-risk patients and weighing the risks and benefits.

GORSHEIN: I have been using it increasingly, as well, in the past 6 to 12 months. For me it’s a more attractive option, potentially, for standard-risk patients, if they’re relatively young and have a good performance status. With high-risk patients, I tend to talk about that vs KRd [carfilzomib, lenalidomide, and dexamethasone], just because of the small sample size in the GRIFFIN [trial] for the [patients with] high risk.1,2

PREET: I usually use quadrplet therapy in high-risk patients, and it also depends on whether I get the insurance approval for the medication; that’s a problem here. Other than that, triplet therapy has worked very well in a lot of patients. The patients who have been newly diagnosed are mostly going on quadruplet therapy, [whereas] the previous ones are on triplet therapy.

CHAWLA: I have used the 4-drug regimen also. I recently had a younger patient in his 40s with high-risk disease, and he had an excellent response to the quadruplet. In the past year I have been using it more and more but for the high-risk younger patients.

USMANI: Would you all agree with [Dr Rotkowitz that] second-line use is mostly triplet regimens? I think that debate is beyond discussion now because we have so many triplets that have demonstrated good efficacy compared with [giving only] 2 drugs.

What would you think about picking one regimen vs the other based on renal function or dose adjusting some of the drugs based on renal function? Do you think about whether the renal function issue is due to a nonmyeloma reason vs due to myeloma?

SHANI: Does the patient have any comorbid conditions [such as] diabetes and hypertension?

USMANI: The patient did have CKD [chronic kidney disease] stage III at baseline. They did have hypertension for the past 15 years. That is another reason for this patient to have the renal insufficiency beyond myeloma. Do you have thoughts about [your choice of] lenalidomide or pomalidomide?

SHANI: I would reduce the lenalidomide, obviously, but [I would] definitely use bortezomib and dexamethasone, and maybe daratumumab.

USMANI: You don’t need to adjust daratumumab for renal insufficiency.

STEINBERG: Maybe daratumumab/CyBorD [cyclophosphamide, bortezomib, and dexamethasone] rather than an IMiD [immunomodulatory drug].

USMANI: I would think about daratumumab/CyBorD. I think it’s a reasonable thing to start patients on, especially if when one feels that the renal function [issue] is primarily because of the myeloma burden, before switching the cyclophosphamide to an IMiD.  

CASE UPDATE

Two years later, the patient continued on lenalidomide maintenance. On routine follow-up, the patient reported having mild fatigue but continued to work full-time. Her bone marrow plasma cells, light chains, and M protein levels were rising. Her kidney function was worsening (now stage IV CKD).
CASE UPDATE

USMANI: We can start discussing this case in a bit more detail. The patient had a relapse after 2 years. She was on lenalidomide maintenance when she was found to have worsening renal function, and the restaging shows 37% bone marrow plasma cytosis now. The M spike and light chains are going up fairly rapidly, so they get worked up.

Test | Value (reference)
---|---
**Biopsy** | 
Bone marrow abnormal plasma cells | 37%

**Laboratory results** | 
Calcium | 10.9 mg/dL (9-10.5)
Serum creatinine | 1.9 mg/dL (0.6-1.3)
Creatinine clearance | 28 mL/min
Hemoglobin | 8.2 g/dL (13.5-17.5)
IgA λ free light chains | 300 mg/dL (0.57-2.63)
M protein | 3.5 g/dL (IgA λ)
Albumin | 2.8 g/dL (3.3-5.7)

**Imaging results** | 
Skeletal survey | No additional lesions

**CASE UPDATE**

The patient received DPd (daratumumab, pomalidomide, and dexamethasone) with a best response of VGPR. One year later, a second relapse was discovered. Her kidney function continued to decline.

USMANI: They start DPd and then they get to VGPR, and they [maintained their response] for a year before they have another relapse. Now their kidney function is declining further. The serum creatinine level is 2.3 mg/dL, creatinine clearance has declined to 20 mL/min. I think we are going to face some interesting choices for the next line.

**DISCUSSION QUESTIONS**

- How often are your patients triple exposed (ie, proteasome inhibitor [PI], IMiD, anti-CD38) at second relapse?
- Now that this patient has relapsed on DPd in the second line, what are the unmet needs for this patient?
- How would a switch in mechanism of action address that unmet need?

USMANI: This patient is now PI, IMiD, and anti-CD38 exposed after the second relapse, and this patient relapsed on DPd in the second line. Just looking at this case, how often do you see these kinds of patients? And when you do see them, what are your thoughts? What are the areas of unmet need for patients like this? They’re clearly IMiD refractory now because they have progressed on lenalidomide and pomalidomide. They’re anti-CD38 refractory. They’re PI exposed but not refractory.

STRAUSS: I would love to put the third-line patients on CAR [chimeric antigen receptor] T-cell therapy, but it’s been very hard for us to get spots. There’s a huge waiting list. Absent that, other BCMA [B-cell maturation antigen]–targeted therapies like belantamab mafodotin [Blenrep] are a good option. I’ve used selinexor [Xpovio].

PREET: I had one patient who progressed on multiple regimens, and she was in very poor health. I used bortezomib and cyclophosphamide, and somehow the cyclophosphamide did help us a lot. She was in a nursing home and was not ready to pay for expensive medications.

USMANI: That’s doable. If they haven’t seen bortezomib in a while and they haven’t seen an alkylator in a while since they got melphalan [Alkeran], CyBorD would be a reasonable choice for this kind of a patient.

ROTKOWITZ: I’d love to send these patients for idecabtagene vicleucel [ide-cel; Abecma] or ciltaacetabtagene autoleucel [cilta-cel; Carvykti], but there are no spots and no availability. There are local/regional clinical trials with teclistamab or talquetamab with a bispecific antibody, which I think would...
be great for these patients. My No. 1 rule is don’t volunteer for anything. Don’t get involved in things that are going to make your life more difficult, and it’s very difficult to get belantamab in the community.

The ophthalmologic necessity for follow-up is very difficult to try to maintain. So if the patients are not candidates for a bispecific antibody, then you start looking at other agents for multiple-relapsed disease: ixazomib [Ninlaro], elotuzumab [Empliciti], and selinexor a bit later down the line. Or you try to recycle something.

I tend not to use another CD38 after daratumumab, so I wouldn’t use isatuximab [Sarclisa]. The patient already got carfilzomib, so you’re pretty limited if the patient can’t go for a clinical trial, but you may try to look at other novel recycling of some other kind of combination that’s there.

USMANI: Has anyone treated patients with belantamab mafodotin in their clinical practices, and what have been their experiences?

STEINBERG: I gave it to one patient who had received 7 prior regimens, and the medication was just approved, and she responded to it. I was really happy. The problem was, it was a heroic effort just to try to get it started. We had to find an ophthalmologist who felt they could be onboard with this, and then apply for the REMS [Risk Evaluation and Mitigation Strategy]. I had to enroll her in the REMS on her [behalf]. It was very frustrating. Then we had to get the ophthalmologist’s [document], then upload it. It was very frustrating, but the patient did respond.

USMANI: That’s good feedback. The theme that I’m hearing is we need more mechanisms of actions for those kinds of patients. Our options become limited. And then trying to get them to CAR T-cell therapy or trials [of bispecifics], if possible, is something that many of you would consider; but with CAR T cells, we are stymied because there are only so many slots.

We are hoping some of that will be mitigated now that ciltacel is approved. So we will have at least twice as many slots; maybe instead of 1 per month, maybe 2 slots per month at each of the transplant centers. This patient gets VRd followed by lenalidomide [maintenance], and then they have their first relapse. They forgo [autologous stem cell] transplant. Then they get DPd after second relapse. And then we talked about all these different options.

This patient is a 73-year-old with worsening renal function now. Beyond the mechanisms-of-action discussion, I think there are so many other [issues] that we can talk about: patient comorbidities, toxicities to prior therapy, performance status. And do you change the mechanism of action when you get to that relapse? Then the co-pays; that’s a challenge.

Dr Rotkowitz brought up issues with care coordination with the eye care specialist [when using] belantamab mafodotin.

GORSHEIN: I’ve had 1 patient who had a good response to [belantamab] after 6 or 8 weeks, but the logistics of it and the frequent visits with an ophthalmologist—overall, the treatment and the associated [issues] with it just became too cumbersome for the patient. He chose to go off the therapy but had a partial response to treatment after about 2 or 3 cycles.

USMANI: The thing with belantamab, if someone is going to respond or have eye issues, you’ll know within the first 2 doses. If they’re not having any response after 2 doses, the likelihood of getting a response is low. If they’re not having eye symptoms after 2 cycles, it’s likely they won’t get them. If you’re going to go that route, it’s a lot of work on the front end.

What I’ve done with my patients is give those first 2 cycles to see what’s happening. If they’re responding [and not having] eye symptoms, I keep on going. If they’re responding, with eye symptoms, I back off and let them rest. We’ll come back a few weeks later with dose attenuation. If they haven’t had a response and have eye symptoms, there’s no point continuing belantamab mafodotin. That’s how I approach that. Right now, we don’t have any bispecifics that are FDA approved, so outside clinical trials if patients are running out of mechanisms of action, I would think about belantamab. I agree, it’s a logistical challenge, trying to get that going.

The patient was started on XVd (selinexor, bortezomib, and dexamethasone) based on her worsening renal impairment, del(17p) status, and prior therapies. She achieved a VGPR.

USMANI: This patient—[because she] had worsening renal impairment and del(17p) and based on prior therapy—was XVd. She had bortezomib exposure but was not refractory, and she hadn’t received a PI in a while. She is being given weekly selinexor along with it, and she got to a VGPR.

DISCUSSION QUESTIONS

- What is your experience with selinexor? Have you used it in combination(s)?
  - What schedule/dosage was used?
  - In which clinical scenario(s)?
STRAUSS: I used it once in combination with carfilzomib and dexamethasone, and [the patient had] a very bad complication from the combination. I think he had a TMA [thrombotic microangiopathy] from the carfilzomib. He recovered, fortunately, and then switched to XVd, and he did OK with it. He tolerated it but then progressed after 6 months or so. This was third line.

GORSHEIN: I’ve used it also, with pomalidomide and carfilzomib, fourth line and fifth line. I used selinexor, pomalidomide, and dexamethasone [XPd] when the patient wanted to maintain their quality of life. They like the all-oral option, as well, with the weekly dosing of selinexor, and they’ve been on it now for 3 or 4 months. So far, they’ve had a partial response and are tolerating it relatively well.

DISCUSSION QUESTIONS
• How do you counsel patients who will receive selinexor?
• If you use selinexor, what steps and supportive care do you routinely perform to help with tolerability?
• What is your approach to dose reduction?
• What is your approach to nausea/vomiting prophylaxis and hydration?

STRAUSS: I had worked at a place where it was given a lot, and though I didn’t personally initiate it, I saw a lot of patients who were on it. I have a lot of experience in that regard, and GI [gastrointestinal] toxicity was one of the big things I would caution the patients about [From the Data]. Be prepared to have antidiarrheals available. That was the biggest take-home I got from my experience with the drug.

SHANI: Dr Steinberg, why weren’t you initiating it?

STEINBERG: Part of it was...I preferred other medications that I felt more comfortable with. For example, we haven’t discussed carfilzomib. This patient wasn’t getting carfilzomib. I probably would have dipped into that well instead. I just felt more comfort with that. The other thing is with an oral drug, sometimes they’re hard to get and you get these gigantic co-pays that patients have to pay. There’s the financial toxicity I would warn the patient about. For those 2 reasons. That’s why, for example, with the belantamab patient, in many ways I preferred the IV option as opposed to oral.

SHANI: You never know whether they are taking it, especially when there was severe nausea and vomiting.

ROTKOWITZ: I would just add that antiemetics are really important. You need to have those onboard. I think [you need] diarrheal prophylaxis and then meticulous cytopenia management. Dose modifications are sometimes warranted to keep the patient on the drug, and you need to monitor their blood counts closely and make sure the nurse practitioners are following up with them very closely.

USMANI: Would you do that early on as you’re starting treatment and then back off from that more intensive approach?

ROTKOWITZ: Absolutely. I do the same in diffuse large B-cell lymphoma, as well, for the patients after multiple lines of therapy. I think the toxicities tend to come earlier, rather than cumulatively, for this drug. I think if the patients are tolerating [the treatment] well, I feel comfortable backing off a little bit.

CHEUNG: My biggest concern for this patient is the renal disease. With selinexor, [there will be] nausea, vomiting, diarrhea; it is a setup for disaster. You need a patient to adhere [to not only treatment] but also follow-up and reporting, and be able to maintain hydration.

FROM THE DATA

In the phase 3 BOSTON trial (NCT03110562), the most common grade 3 or higher treatment-related adverse events (TRAEs) were thrombocytopenia (39% with selinexor, bortezomib, and dexamethasone [XVd] vs 17% with bortezomib and dexamethasone alone [Vd]), anemia (16% with XVd vs 10% with Vd), fatigue (13% with XVd vs 1% with Vd), and nausea (8% with XVd vs 0% with Vd). Dose modifications were required in 89% of patients receiving XVd vs 76% with Vd, whereas TRAE-related discontinuations occurred in 21% of those receiving XVd vs 16% of those receiving Vd.
Lancet Blood

One of the therapies that we haven’t mentioned too much, and you brought it up, was alkylators. Or just giving an alkylator too much, and you brought it up, was alkylators. Or just giving

STEINBERG: That makes sense. It’s an all-oral option. I think that’s very reasonable.

USMANI: I think Dr Steinberg brought up the same point about some alternative options [because] carfilzomib hasn’t been used for this patient. Neither has an alkylator.

DISCUSSION QUESTIONS

• Based on available clinical trial data, FDA-approved indications, and the National Comprehensive Cancer Network multiple myeloma guidelines, where does selinexor triplet therapy fit into the treatment landscape?
• What changes, if any, have you made to your management of relapsed/refractory multiple myeloma over the past year or so?

USMANI: Looking at how the landscape for first-line treatment is evolving, where do you feel selinexor will get used mostly, looking at the various combinations in the STOMP study [NCT02343042]?5-7

GORUSU: Maybe XPd. Because practically speaking, if we are talking about in the third-or-so line, we must have likely used the PI, and daratumumab must have already been used. Somehow, a little bit, trying to be careful with carfilzomib. If I were to pick, I think I would go within the XPd space.

USMANI: That makes sense. It’s an all-oral option. I think that’s very reasonable.

STEINBERG: One of the therapies that we haven’t mentioned too much, and you brought it up, was alkylators. Or just giving this patient an IV DCEP [dexamethasone, cyclophosphamide, etoposide, and cisplatin] or VD-PACE [bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide], or something [similar].

I don’t think the renal dysfunction would necessarily exclude the patient from getting melphalan or high-dose chemotherapy, to at least to give this patient some breathing space, at least temporarily, and then put them on some kind of maintenance. Then it’s time to think about what you want to give them.

USMANI: I think that’s a good point. The patient is essentially alkylator naïve, so you can think about employing some old-fashioned chemotherapy, especially if they’re presenting with high-burden disease and you can modify doses of treatments based on renal function as well.

REFERENCES


Clinical Commentary: Managing Adverse Events From PARP Inhibitors in Advanced Ovarian Cancer

**EVENT SUMMARY**

At a live virtual event, Saketh Guntupalli, MD, discussed with participants the role of PARP inhibitors in the first-line setting for patients with advanced ovarian cancer. Looking at several studies that identified the efficacy of the 3 main PARP inhibitors, rucaparib (Rubraca), olaparib (Lynparza), and niraparib (Zejula), Guntupalli highlighted their effectiveness for this patient population. However, patients with advanced disease may face challenges while on these therapies, and according to Guntupalli, it’s important to address these adverse events (AEs). Moreover, he discussed ways to look at the whole patient to find suitable methods, such as dose reduction, to best help them.

**Saketh Guntupalli, MD**

Associate Fellowship Program Director, Gynecologic Oncology Assistant Residency Program Director Assistant Professor University of Colorado Cancer Center Aurora, CO

**Adverse Events on PARP Inhibitors**

It’s interesting [to me that] the 3 PARP inhibitors, [rucaparib, olaparib, and niraparib], seem to act a little differently on different myeloid lines. For example, with olaparib, there’s a lot of anemia, and it’s affecting that red blood cell myeloid stem line. With niraparib, we see a lot more thrombocytopenia, whereas with rucaparib we’re seeing more liver function test [abnormalities] and leukopenia.

It’s interesting to me that the 3 PARP inhibitors that theoretically work on the same pathway each have their own unique issue, and that’s important, because managing that is what drives some of the symptomatic toxicity.

You’re going to see a lot of neutropenia with niraparib, but in the combination of olaparib plus bevacizumab we don’t see as much.

Nausea is worse with olaparib, and it seems to have some type of GI [gastrointestinal] first-pass effect that’s worse. I don’t see a lot of vomiting, at least in my practice. It’s mainly nausea, and fatigue across the board is bad. But I think that fatigue is being driven by anemia. There is not much hypertension with olaparib, maybe a scant amount with niraparib, and by adding bevacizumab, we see it increases [Table 1-3].

GI toxicity, like nausea, [is also challenging], but the most challenging in my experience is thrombocytopenia. That has been difficult to manage because [transfusion] is a temporary fix. However, patients will push to stay on the PARP inhibitors because they’d rather take a pill than sit in an infusion center for a couple of hours every few weeks.

**Deciding Which PARP Inhibitors to Use**

One of the things I do is look at the patient and see how they did [with] platinum-based chemotherapy. For example, if somebody [didn’t respond well] and had bad liver toxicity, I would steer [them] away from rucaparib, because that’s going to [increase] the LFG profile. [In comparison], if somebody started with high-volume disease and had a high platelet [count], we see that because it’s an acute phase reactant, I might be more inclined to use niraparib because they must have disease volume there. I would probably not use niraparib [for] somebody who had profound carboplatin-induced thrombocytopenia.

Patients are different, but I would use olaparib instead. In somebody who is a little older, a little more prone to fatigue, I’m probably less likely to use olaparib. A lot of factors go into the decision about which inhibitor you’re going to use, but I think age is a big part of it.

Are patients going to be able to tolerate that toxicity? If you have a 52-year-old BRCA-positive patient with metastatic ovarian cancer, I’d probably be as aggressive as possible and treat through the niraparib toxicities. Whereas if I have an 82-year-old patient with cancer [who has] wild-type BRCA with more medical problems, I might proceed with olaparib. So I try to look at the patient [holistically] to make that decision.

If this is somebody who developed [a] platelet [count] of 80,000 μL on cycle 2 [on] day 1 of treatment after 1 cycle of chemotherapy, that would make me nervous. I would say cytopenias from that treatment are bad. Regarding the patient’s performance status, I look at that, particularly in an older patient. For example, should we be using PARP [inhibitors] in an 85-year-old who has multiple comorbidities? Sometimes getting them through chemotherapy is a win.

Financial toxicity [is also a consideration because] for some patients these drugs are not going to be completely covered by insurance. Quality of life overall is incredibly important. I have a patient who was on a PARP inhibitor...
who was nauseated every day, and she kept losing weight. She said, “I have no appetite. I want to throw up all the time.” Is that any way to live? But there are some ways we can work with that, and we talked about decreasing the dose and about timing of medication. These are vital conversations to have with your patients.

Managing Toxicities From PARP Inhibitors
[To avoid some toxicities we are seeing], individualized niraparib dosing in the maintenance setting is important. This is what we call our weights and platelets, [and it] gives you some options to get patients through that initial toxicity. If their baseline weight is greater than 77 kg and their platelet [count] is above 150,000 μL, we can start at 300 mg once daily. If [their baseline weight is less than 77 kg and their platelet count is below 150,000 μL], we want to start at a lower dose.

For maintenance treatment of patients with ovarian cancer, [they] should start on a regimen with niraparib no less than 12 weeks after their most platinum-containing chemotherapy regimen. Then [make] dose adjustments for those AEs from niraparib. You want to go down; that’s your first dose reduction. You go down to 100 [mg]. At 100 [mg], you have to think about benefit analysis. For olaparib at 300 [mg twice a day], [reduce to] 250 [mg], then 200 [mg]. So for olaparib, it’s a [50-mg reduction]. The reduction for niraparib is a 100-mg reduction. Those are things to keep in mind.

Checking for Homologous Recombination Deficiency (HRD) Status
The only approved test is the Myriad my Choice HRD test. That is a true HRD score, and that’s important to keep in mind.4 When we look for HRD, we’re looking at 3 components: the loss of heterozygosity, large-field translocations, and large-scale translocations, as well as the balance among them. That’s what Myriad uses, and they generate the score that determines whether the patient has HRD. We know enough about the genetics of ovarian cancer to know what is driving the HRD status is the loss of heterozygosity.

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A lot of [individuals] will use loss of heterozygosity as a surrogate marker, and that’s what they did in [the] ARIEL3 [study] [NCT01968213] with rucaparib. They used that as their surrogate marker for HRD status. I think that’s reasonable, and I believe other companies are giving you a loss of heterozygosity score.

I have used PARP [inhibitor] therapy in patients who [have] HRD negativity. If they’ve had a complete response, if they have a normal [level of] CA125 [cancer antigen 125], if their posttreatment scan [result] is negative, I will have a discussion with them. We then go through the PRIMA study [NCT02655016] data, and we talk about the fact that most of these patients are going to [have recurring disease]. If we use it in the up-front setting, it may be difficult to get in the recurrent setting because an insurance company could say, “Well, you already used this.”

There are some patients who want it, there are some patients who say, “I want to try everything now and keep this at bay,” and there’s a subset of patients who are going to keep the disease at bay in the up-front setting. I don’t use it in all patients. I use it in patients with BRCA in their cancer and almost all my patients [who have] HRD. That’s why that marker is so important.

**Adding Bevacizumab to Treatment**

Bevacizumab has a couple of roles to play in treatment. The first is in patients [with suboptimal cytoreduction], because we know in [the] subset of patients in the GOG-0218 [NCT00262847] and ICON7 [ISRCTN91273375] studies, those patients were the ones who benefited most.

Let’s say the patient had high-volume disease. We’re able to get most of it, but a decent amount was left behind for whatever reason. I’d probably add bevacizumab to the therapy. Another [patient for whom] I might consider adding bevacizumab is one with stage IV cancer. For example, I would add it [for] someone who had pleural effusion [or] disease in the lung or [for] someone with high-volume ascites, because it is therapeutic for that patient and dries up the ascites quickly. The trade-off, however, is the hypertension and [that a patient with] a [lot] of ascites probably has a fair amount of disease on their bowel.

It makes me a little nervous about giving bevacizumab to someone and then [seeing them have] a bowel perforation. But those are generally the patients [for whom] I will use [bevacizumab] in the up-front setting.

**Dose Management**

One thing we try to do, because we don’t want to lower the dose, have some nausea, and not get the benefit, concerns timing. So if they’re on 300 mg of niraparib, we may break that dose into 2.
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Kd=Kyprolis (carfilzomib) and dexamethasone