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Levy Discusses Treatment Options for ALK-Rearranged NSCLC

### CASE

- A 55-year-old woman presented with worsening dyspnea and persistent dry cough.
- Smoking history: prior smoker (<5 pack years)
- Medical history: atrial fibrillation
- Imaging revealed a lung mass with metastases to intrathoracic lymph nodes and liver.
- Brain MRI: several subcentimeter intracranial lesions consistent with metastatic disease; she was asymptomatic from her brain metastases.
- Liver biopsy: consistent with lung adenocarcinoma
- Tumor next-generation sequencing (NGS; FoundationOne): ALK (EML4-ALK translocation) positive; negative for EGFR, ROS1, BRAF, KRAS, NTRK, MET, RET
- PD-L1: 0%

### POLLING QUESTION

During a live, virtual event, Levy asked, “What systemic therapy are you most likely to recommend for this patient with ALK-rearranged, metastatic non–small cell lung cancer with central nervous system metastasis?”

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### Targeted Oncology™: What do the National Comprehensive Cancer Network guidelines recommend for ALK-rearranged non–small cell lung cancer (NSCLC)?

**LEVY:** Alectinib [Alecensa], brigatinib [Alunbrig], and lorlatinib [Lorbreon] are all category 1 for first-line indication.¹ There are other recommendations—ceritinib [Zykadia] is a category 1. “Useful in certain circumstances” is the designation for crizotinib [Xalkori]. But I think the ones that we wrestle with, and the ones that we think about, are alectinib, brigatinib, and erlotinib.

What are the data behind alectinib for this patient population?

The ALEX trial [NCT02075840] was an ALK fusion-positive patient population.² Interestingly, immunohistochemistry [IHC] was done. IHC is a wonderful test for ALK, by the way. It has a high concordance rate with NGS. So for a rapid readout, we do an IHC for ALK sometimes if we suspect it because you can get your answer within a day. These patients were randomly assigned to alectinib 600 mg twice a day or crizotinib 250 mg twice a day. The primary end point was progression-free survival [PFS].

The PFS for alectinib...is 3 years.³ That’s the median time that they’re on drug before they progress. The median overall survival [OS] hasn’t even been reached yet, with 48 months of follow-up. The 5-year OS rate is 62.5% [HR, 0.67; 95% CI, 0.46-0.98; \( P = 0.0376 \)].³ That’s incredible. I know this is a rare patient population, but when I started in lung cancer, the median OS for all patients was 12 months. This is what gets things moving and moves the field forward. The PFS rates [for patients with] baseline central nervous system [CNS] metastases were 40% at 3 years with alectinib vs 2.1% with crizotinib.³

For those of you who treat breast cancer and some other tumors, it’s certainly not as good as that, but we’re making a lot of headway. If you look at the OS by subgroup, everyone seemed to benefit. This is a univariate analysis that we see in any study, where it breaks down essentially different patient populations to see whether one particular patient population had a more pronounced benefit of the drug, the experimental arm, alectinib vs crizotinib. Everyone seemed to benefit.

Can you discuss the ALTA-1 trial (NCT02737501) of brigatinib?

This was another study that was recently published, about 2 or 3 years ago, similar to the ALEX study with a similar
comparator arm. Brigatinib, started at 90 mg and then escalated to 180 mg, was compared with crizotinib. We saw an improvement in PFS; the HR was 0.48 [95% CI, 0.35-0.66; \( P < .0001 \)].\(^5\) I think the Kaplan-Meier curves are very similar to [those of] the ALEX trial.

If you look at the brain metastases at baseline, that group seemed to derive a significant benefit with brigatinib vs crizotinib.\(^6\) I’m not a big brigatinib user, but I understand the rationale, based on these ALTA-1 data. If we look at intracranial PFS for those patients with brain metastases, these are small numbers of patients, but the HR is 0.29 [95% CI, 0.17-0.51; \( P < .0001 \)].\(^5\) For those who got brigatinib vs crizotinib, median PFS was 2 years [vs 5.6 months, respectfully]. So essentially, brain metastases were under control, if those receiving brigatinib had them at baseline, for close to 2 years before there was progression in the brain.

The objective response rate (ORR) to brigatinib was 74% vs only 62% with crizotinib [OR, 1.73; 95% CI, 1.04-2.88; \( P = .0342 \)].\(^6\) I think the challenge is we don’t have long-term follow-up with ALTA-1 the way we do with ALEX.

The ORR in the brain with brigatinib vs crizotinib was 78% with brigatinib and only 26% with crizotinib [OR, 11.67; 95% CI, 2.15-63.27; \( P = .00014 \)], it’s remarkable to see those data.\(^6\) We don’t have OS maturity the way we do with ALEX, so we’re all waiting to see how these data pan out.

**How did patients respond in the clinical trial of lorlatinib?**

The CROWN trial [NCT03052608] is the third chapter of next-generation ALK tyrosine kinase inhibitors [TKIs] vs crizotinib.\(^7\) We at least have 3 trials that have the same comparator arm of crizotinib, so we can do what we’re never supposed to do, which is cross-trial comparisons, to see which drug may be better. Phase 3 CROWN data were in patients with stage IV, ALK-positive disease. They were allowed to have CNS metastases at baseline. They were randomized to lorlatinib, 100 mg a day, vs crizotinib. The primary end point was PFS.

CROWN had the most pronounced benefit we saw compared with brigatinib and alectinib. If you compare the HRs and you see they diverge more dramatically than in the alectinib data and the PFS. The PFS HR was 0.27 [95% CI, 0.18-0.39].\(^7\) These are cross-trial comparisons, so it’s tough to know whether lorlatinib is better than alectinib or brigatinib, but this is the most pronounced PFS we’ve seen in any study that compares a next-generation ALK TKI to crizotinib.

The ORR with lorlatinib was 77%, and the median duration of response has not been reached.\(^8\)

There were 3 complete responses.\(^7\) The lorlatinib intracranial ORR was 66% vs 20% with crizotinib. These are a small number of patients who were enrolled, and this is only a subset of the patients who were enrolled in the entire study. For those patients who didn’t have brain metastases, who received lorlatinib, 99% of them did not have brain metastases at 3 years, which is better than any data we have with brigatinib or alectinib so far.\(^8\) If you look at the patients with brain metastases who received lorlatinib, about 75% of them at 3 years still had control in the brain. The OS curves overlap, but we’ll see what happens here over time.\(^7\) It’s very early, but we’ll have to see how it all shakes out.

**Can you summarize ALEX, ALTA-1, and CROWN?**

Looking at median PFS between these 3 studies, ORR, intracranial response rate, it looks like interestingly enough that CROWN and ALEX have a little bit of an edge over ALTA-1.\(^3,5,8\) But the median PFS for baseline brain metastases has not been reached in CROWN, and I think that curve is the one that everyone talks about. You’re able to protect the brain if you receive lorlatinib.

For the adverse events [AEs] between alectinib, brigatinib, and lorlatinib—every drug has different toxicities—with alectinib, we see a lot of liver function test [LFT] abnormalities and peripheral edema. For brigatinib, we see some creatine phosphokinase elevations, and LFT abnormalities.\(^3,8\) Then lorlatinib has a different set of AEs that are worth noting. Certainly, the cognitive effects in the hyperlipidemia are real, as somebody who has used this drug before.\(^7,8\)

**CASE UPDATE**

- The patient received lorlatinib; radiation therapy was initially deferred.
- Four weeks after initiation of lorlatinib:
  - Repeat MRI showed resolution of brain metastases, and patient had a systemic response.
  - Patient reported feeling confused and having difficulty with memory/multitasking for the past 10 days.

**How do you manage lorlatinib-emergent CNS AEs?**

You need to monitor at baseline and schedule a follow-up visit after the first 6 weeks.\(^3,11\) [For management], you need to do an MRI, refer to a psychiatrist or therapist if they develop CNS metastasis, review concomitant medications, and consider holding for grade 1 events [and resume at the same or lower dose after recovery]. But for grade 2 and 3, maybe resume at a reduced dose upon recovery. I usually hold and resume at a lower dose.

The first dose decrement is 75 mg, second is 50 mg, and then permanently discontinue. I’ve had a couple of patients who have had major cognitive deficits from this drug. We were able to get them through, and I think [it’s important to be] engaging the family members and warning [them] that this may
happen, because the patient can be completely unaware that this is happening. So we usually get patients through, and some patients do fantastic on the drug without it. We don’t know why some patients develop cognitive deficits and why others don’t. The other thing is hyperlipidemia with lorlatinib can be an issue. I always start a patient on a statin when I start lorlatinib.

**CASE UPDATE**

Lorlatinib was held for 2 weeks and resumed at 75 mg daily after patient reported complete resolution of symptoms.

**REFERENCES**


A 75-year-old man presented with intermittent right hip pain, but his physical exam was unremarkable. His clinical workup showed a prostate-specific antigen (PSA) level of 32.6 ng/mL, and his bone scan and abdominal/pelvic CT scan were negative. A transrectal ultrasonography biopsy showed he had a Gleason score 4 + 4 and Grade Group 4. He was diagnosed with stage T2N0M0 and an ECOG performance status of 1.

External beam radiation therapy plus androgen-deprivation therapy were initiated and planned for 18 months, but there was undetectable PSA level at 6-month follow-up and the testosterone at castration level was asymptomatic. However, 6 months later the patient developed new hip pain and urinary frequency, with a PSA level of 29.4 ng/dL and testosterone level of 10 ng/dL.

The patient was now considered metastatic and castration resistant, and he began treatment on enzalutamide (Xtandi) at 160 mg by mouth daily. Four months after beginning enzalutamide, the patient’s PSA level decreased to nadir of 3.9 ng/dL; after 8 months on enzalutamide, the patient had a PSA level of 60.7 mg/mL. He was started on docetaxel (Taxotere) at 75 mg/m² intravenously (IV) every 3 weeks and daily prednisone by mouth every 12 hours. After 6 cycles, the patient developed bilateral digital neuropathy and docetaxel was held. Then after 3 months, he had a rising PSA and new back pain.

**SLOVIN:** About a third of you want to repeat the next-generation sequencing [NGS] and cell-free DNA testing, but these are not mutually exclusive. You certainly could do both. Only 17% want to look toward the lutetium, which is very surprising because we are constantly deluged with people coming in and saying well, when is this miracle drug going to come to your institution? So,
I’m surprised that only about 17% of people are interested in doing that. We got no votes for radium-223 [Xofigo], so it seems that radium may be falling out of popularity.

Anybody have any thoughts of what else they could do, or would like to do? There’s always [putting the patient on a] clinical trial, that would be reasonable.

PETRYLAK: [Radium] is clearly contraindicated for liver metastases at that point. It’s not going to help because radium doesn’t go [to the liver]. But one choice that’s not [presented] here, which I like using in this situation, is cabazitaxel [Jevtana] along with carboplatin. This is aside from [doing another biopsy] to see if [the cancer has] converted to a small cell type, which, given the elevated PSA [level], it probably hasn’t, although you can see biclonal disease [when] looking for MSI status or other DNA repair deficiencies if [the patient] develops a somatic mutation.

SLOVIN: I would agree, and sometimes, if [a patient is somewhat] frail, you could possibly get away with [giving the] carboplatin weekly, at 3 weeks on and 1 week off, which is reasonable to do. I have, on rare occasions, used paclitaxel even [in patients] who have neuropathic problems and I’ve managed [to give it] at low doses; sometimes giving [paclitaxel] at a low dose or weekly can [deliver] the drug [successfully]. Does anyone have any other comments?

ZHU: I think just based on the studies [¹⁷⁷Lu-PSMA-617 (Piluvicto)] also failed at least 1 second-generation [androgen receptor (AR) agonist] and 1 [chemotherapy regimen]. With cabazitaxel you can get a median progression-free survival [PFS] and have less benefit, so I want to say this patient also has indication of prostate-specific membrane antigen [PSMA] positive lesions scan on a PSMA scan.

SLOVIN: [Perhaps] you remember that at a recent American Society of Clinical Oncology [ASCO] Annual Meeting, Michael Hofman, MD, from Australia, was talking about his phase 3 trial of [¹⁷⁷Lu-PSMA-617 vs cabazitaxel] [TheraP, NCT03392428]. He initially had shown, at the 20-month mark, that there had been an improvement in radiographic PFS and overall survival [OS].¹ [It was hoped that this benefit would continue, but] at this year’s ASCO meeting, the data showed that there was no [longer a] difference in OS.²

And the major question, of course, is how do you strategize? Do you give cabazitaxel first and then [¹⁷⁷Lu-PSMA-617]? Do you give [¹⁷⁷Lu-PSMA-617] first and then cabazitaxel? Just as a point of interest, I want to note that] sometimes everybody gets excited about phase 3 [trial results] very early, because [the studies] often use radiographic PFS as a surrogate marker for OS. However, in this case, there was no significant difference [in OS].

PETRYLAK: I look at how fast the disease is moving and whether the patient has visceral disease or not. [I also look at the] patient’s overall fitness. I think you [should consider whether their] fitness [is influenced more by] the metastases or by some other underlying condition. We’ve seen great improvements in bone pain [management and] great improvements in performance status in patients who respond but [were in] quite bad shape to begin with, so I think you’ve got to decide that carefully. And [increasingly], we’re seeing financial considerations [affecting] our patients.

The drug may or may not be approved by the insurance company. We’re seeing that particularly with [AR-targeted drugs]. You have to use your gut [to make this decision]. [Is the patient] progressing rapidly? Do they need chemotherapy? [Another thing to consider is that] we don’t know what the effect of [¹⁷⁷Lu-PSMA-617] is going to be on marrow suppression [and] whether the patient can get cabazitaxel or other myelosuppressive agents.

SLOVIN: At the ASCO meeting, I had to give a commentary, and a gentleman in the audience protested, “[The patients are] going to be dead in 10 years [anyway, so long-term toxicity does not matter].” [But] the reality is that [these patients] are not dead in 10 years. I have had patients with Gleason scores of 8 or 9, some of whom have been alive and kicking for 20 to 25 years. And [such patients] are not [rare]. A lot of patients are like that now, and we are affecting peoples’ lives, but we don’t know the long-term toxicity.

Does anybody else want to [share] what factors you would look at?
KAPPEL: I think [Dr Petrylak] brought up [several important] points. Patient preference, financial [considerations], logistics, [and the] nature and pace of progression [are] all standard [considerations] among all cancers. But [a particularly important] [consideration that he mentioned was] comorbidities. Prostate cancer may be one of those unique [cancers] where we’re dealing with older guys who have more comorbidities [and] who aren’t going to be able to tolerate some of these therapies. Their ability to take multiple lines of therapy [may be less than that of other patients with other cancers]. A lot of these patients are in their 80s, so they’re not eligible for multiple lines of therapy.

SLOVIN: You’re absolutely right.

MO: I [would take] the patient’s symptoms and their performance status [into consideration]. I totally agree with Dr Kappel. I [would consider] going to cabazitaxel, [and] I would think about decreasing the dose [to] 20 mg because I worry about pneumonitis.

BRAUNSTEIN: The duration of prior response and other comorbidities would be at the top of my list, and the symptoms are [also] important [to consider].

SLOVIN: Yes, I think we’re probably all in accord with these things, but a lot of [the treatment process] depends on patient compliance. There’s no question. I’m [dealing] with patients going to Florida and wanting to get their care there. It ends up [being] difficult to manage these patients.

DISCUSSION QUESTION
A decision was made to start cabazitaxel. What starting dose would you most likely use?
- 25 mg/m²
- 20 mg/m²
- Other

SLOVIN: [In a comparison of] cabazitaxel, either 20 mg/m² or 25 mg/m², vs docetaxel [FIRSTANA; NCT01308567], [researchers] found that the [2 cabazitaxel dosages] were comparable [From The Data]. I think most physicians use 20 mg/m² because it has less toxicity. I personally do not use pegfilgrastim [Neulasta] if I’m using the 20 mg/m²-dose, and I’ve never had any problems with neutropenic fever. [Have you had] any problems when you’ve used [cabazitaxel]?

PETRYLAK: No, I haven’t. [Granted, I’m a little more cautious] and I do use pegfilgrastim, but no, I haven’t had trouble.

The real issue with [cabazitaxel] is diarrhea, [but overall] it’s better tolerated than docetaxel [and causes] less neuropathy. In fact, in patients who need [to maintain] manual dexterity and who are worried about neuropathy, I’ve used this frontline. This is off-label, but I’ve done it that way with fairly good results. In fact, the data from the randomized trial of frontline docetaxel vs cabazitaxel showed no difference in survival, and the neuropathy was [better with cabazitaxel]. And that’s [a facet of the data] that was never emphasized.

SLOVIN: I’m surprised that you are able to give it in the frontline. I’ve never been able to do that.

PETRYLAK: I’ve only tried twice, but I’ve gotten it. This was for 2 [patients] who needed it.

SLOVIN: That’s understandable. Is anybody else using it in the front line?

ZHU: I never use [it in the front line].

KAPPEL: I haven’t used it in the front line. but I want to emphasize that paclitaxel is even worse than docetaxel in terms of neuropathy. These patients have long-term neuropathy. It’s almost crazy to think that their neuropathy gets better because it just doesn’t. And it’s a horrible, horrible toxicity for a lot of people, quite debilitating. And paclitaxel is the worst.

SLOVIN: [According to] the National Comprehensive Cancer Network [NCCN] guidelines on the use of cabazitaxel, you could use 20 mg/m² or 25 mg/m². You could use it with a steroid, [though] I personally don’t. I don’t use growth factor, but I think you need to determine whether [your patient has] been very heavily pretreated and make a decision. [The NCCN guidelines also offer] cabazitaxel plus carboplatin [as an option]. I’ve used that, and I do agree that [the combination] can be gentle relative to either drug.

DISCUSSION QUESTIONS
• Would you give cabazitaxel to a patient who did not tolerate docetaxel well?
• If this patient had completed 6 or more cycles of docetaxel, would your recommendation differ?
• Have you used carboplatin plus cabazitaxel? If yes, please share your experience. In what scenario(s) did you use it?

SLOVIN: Would [anyone here choose to use 177Lu-PSMA-617] or something else? I don’t think it makes a difference
how many cycles [of docetaxel the patient has had]. This [patient] only got 4 [cycles] and had problems. In a case like this, if a patient had very bad neuropathy and I had [177Lu-PSMA-617] available and the patient was, of course, PSMA-avid, I probably would vote for [177Lu-PSMA-617] before giving cabazitaxel.

I think, Dr Petrylak, you and I have both [used carboplatin plus cabazitaxel], and that combination is tolerable. Dose modifications, I think, depend on their [labs] and how the patient is feeling. I [had] a patient who was on docetaxel [and] had a very short-lived response [and] progressive adenopathy, minimal bone but all adenopathy. And I [then used] carboplatin plus cabazitaxel, and, [as assessed] by fluoro-deoxyglucose PET scan, [there was] a 95% response rate in terms of adenopathy regression. I did biopsy [at that point], and there were no actionable mutations. There was no neuroendocrine component, just high-grade prostate cancer. Is there anything you want to [share regarding] your experience with the carboplatin plus cabazitaxel combination?

PETRYLAK: Yes. The recommended dose is 20 mg/m² and [the target] area under the curve is 4 mg/mL min [with carboplatin].5,6 I’ve had good experience with liver metastases with this [combination in] one of our patients, who was on a randomized trial of docetaxel plus or minus [an experimental] drug. [This patient] had liver metastases, and then he progressed in [the] liver. He’d had a good response to docetaxel, initially. And [there is no] neuroendocrine [carcinoma]; he’s been biopsied.

DISCUSSION QUESTION

What is your opinion of the data from the CARD trial (NCT02485691) of cabazitaxel vs an AR-targeted agent?

SLOVIN: [I think we can all agree that the data are] compelling and will influence [our] practice. Everybody seems to be in favor of using the drug.

KAPPEL: [This discussion is] making me relook at chemotherapy in general.

SLOVIN: [Does] anybody have any other thoughts? Dr Petrylak and I like to use cabazitaxel. In terms of how to manage any major toxicities, as I said, I’ve never had to use pegfilgrastim [with] the 20 mg/m²-dose [of cabazitaxel]. I know some people [give pegfilgrastim] routinely. I don’t even give it with prednisone because some of our patients have already been on prednisone from prior chemotherapy. I [might] keep them on 5 mg [after docetaxel [treatment]]; I don’t want to increase it to 10 mg, for example.

[Another question is], how does everybody decide what to tell [patients]? Are we saying is it better, in most cases, if you have metastatic castration-resistant disease after hormone-based therapy, to do another AR-signaling inhibitor, maybe a clinical trial, or go to a second-line chemotherapy? Do you prefer IV [therapy] to oral [therapy for reasons of tolerability]? Does anybody have any thoughts on how they would make recommendations?

PETRYLAK: You can get just as sick with an oral drug as you can with an IV drug, sometimes even sicker. So, it’s more [a matter of] the tolerability [in general]. The [adverse] effect I’ve encountered the most with cabazitaxel recently has been some diarrhea. It [doesn’t happen] commonly, not as much as [with] the 25-mg dose. The 20-mg dose is very well tolerated, and usually the standard treatments for diarrhea [loperamide hydrochloride] and, if necessary, octreotide acetate [are sufficient]. But again, I think it is an incredibly well-tolerated drug.

SLOVIN: My only issue [with] oral medications is the potential interaction with other oral agents.

KAPPEL: [Regarding] steroids, I agree with you. With prednisone, it [can sometimes be] difficult to get people’s [dose] down; [but] you know, there’s no evidence that you need to give prednisone with docetaxel.

FROM THE DATA

In the frontline setting, cabazitaxel monotherapy proved to be more beneficial than chemotherapy in the phase 3 FIRSTANA trial (NCT01308567) that looked at either a 20 mg/m² or 25 mg/m²-dose of cabazitaxel.3 However, while neither dose showed a superior OS benefit when compared with 75 mg/m² of docetaxel, tumor response was improved in patients on 25 mg/m² of cabazitaxel at 41.6% vs 30.9% in the chemotherapy arm. Moreover, there was overall less toxicity for patients on 20 mg/m² of cabazitaxel in comparison to the higher dose.

In the frontline setting, cabazitaxel monotherapy proved to be more beneficial than chemotherapy in the phase 3 FIRSTANA trial (NCT01308567) that looked at either a 20 mg/m² or 25 mg/m²-dose of cabazitaxel.3 However, while neither dose showed a superior OS benefit when compared with 75 mg/m² of docetaxel, tumor response was improved in patients on 25 mg/m² of cabazitaxel at 41.6% vs 30.9% in the chemotherapy arm. Moreover, there was overall less toxicity for patients on 20 mg/m² of cabazitaxel in comparison to the higher dose.
That’s been a debate from the beginning. There is no scientific evidence that [adding prednisone] is better than docetaxel alone.

**SLOVIN:** Yes, you’re right. Does anybody else want to comment [about] a preference for IV or oral [therapy]?

**KAPPEL:** I [prefer] IV over oral [therapy] because [with an IV drug], you know [for certain that] the patient is getting [the drug]. You can evaluate the patient and see how they’re doing. It may not necessarily be the better [out-of-pocket cost] for health care in general but for the patient, it’s the better [out-of-pocket cost]. Patients have a false impression that if [a drug is] oral, it’s going to be better tolerated than an IV drug.

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**REFERENCES**


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1L=first-line; aRCC=advanced renal cell carcinoma; CI=confidence interval; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

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CABOMETYX is indicated for the treatment of patients with advanced RCC.

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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.

Please see additional Important Safety Information throughout and Brief Summary of the Prescribing Information for CABOMETYX on following pages.
Superior PFS and ORR results in the ITT population in the primary analysis¹

Median follow-up time of 18.1 months; range: 10.6-30.6 months²

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Secondary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEDIAN PFS WAS DOUBLED</strong>¹</td>
<td><strong>ORR WAS DOUBLED</strong>¹</td>
</tr>
<tr>
<td>16.6 months CABOMETYX + OPDIVO</td>
<td>8.3 months sunitinib</td>
</tr>
<tr>
<td>VS</td>
<td>(95% CI: 12.5-24.9; n=323)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR</th>
<th>55.7% CABOMETYX + OPDIVO</th>
<th>27.1% sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI: 50.1-62.2; n=323)</td>
<td>(95% CI: 22.4-32.3; n=328)</td>
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</tbody>
</table>

P<0.0001

<table>
<thead>
<tr>
<th>PR</th>
<th>8% CABOMETYX + OPDIVO</th>
<th>4.6% sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=26/323)</td>
<td>(n=15/328)</td>
<td></td>
</tr>
</tbody>
</table>

P<0.0001

*PFS and ORR were assessed by BICR.¹

**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS**

**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 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=11) 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 4.7% (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% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstanted 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 proteinuria, 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 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.
Early and sustained separation of OS curves in the primary analysis

Secondary endpoint

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>323</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>12</td>
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<td></td>
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<td>18</td>
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<td>24</td>
</tr>
<tr>
<td></td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

Final analysis of OS (median follow-up: 32.9 months; range: 25.4-45.4 months): Median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI: 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI: 29.0-NR; n=328); HR=0.70 (95% CI: 0.55-0.90).1-7

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.

Embry-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.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John’s wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

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.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on following pages.

BICR=blinded independent central review; CR=complete response; ITT=intent to treat; IV=intravenous; PFS-2=progression-free survival after subsequent therapy; PK=pharmacokinetics; PO=by mouth; PR=partial response.

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 or nivolumab, 1 (2%) 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.

5.8 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 4.7% (15/320) of patients with RCC who received CABOMETYX and 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 2.9% of patients with RCC. Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 21% (n=4) of the 20 patients enrolled in CABOMETYX with nivolumab who was withheld for adrenal insufficiency, 6 reinstated treatment after improvement of symptoms; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 Proteinuria

Proteinuria was observed in 8% of patients receiving CABOMETYX. 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 and CABOMETYX in patients who develop nephrotic syndrome.

5.10 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX. 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 extraction of a tooth. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks 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.

5.11 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.

5.12 Reversible Posterior Leuкоencephalopathy Syndrome

Reversible Posterior Leukocencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.13 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.

5.14 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.

5.15 Embryo-Fetal Toxicity

Based on data from animals and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. CABOMETYX administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose. Do not initiate CABOMETYX in pregnant women. Cabozantinib administered to pregnant animals caused malformations in rats and visceral variations and malformations 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, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hypocalcemia, 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 491 patients with RCC enrolled in randomized, active-control trials (CELESTIAL, METEOR). 467 patients with RCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), and 156 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE 028).

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.

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grade Grades 1-4</td>
<td>All Grade Grades 1-4</td>
<td>All Grade Grades 1-4</td>
</tr>
<tr>
<td>Percentage (%) of Patients</td>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Asthma</td>
<td>19</td>
<td>4</td>
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</tbody>
</table>
### Table 2. Laboratory Abnormalities Occurring in ≥ 25% of Patients who Received CABOMETYX in CABOSUN

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=78)</th>
<th>Sunitinib (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td>CABOMETYX (n=78)</td>
<td>Sunitinib (n=72)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>19</td>
<td>1.4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>37</td>
<td>1.4</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>23</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>18</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>32</td>
<td>0.8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>9</td>
<td>1.8</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16</td>
<td>0.7</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>25</td>
<td>0.8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
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<td>0.3</td>
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<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>0.5</td>
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<tr>
<td>Hyperbilirubinemia</td>
<td>9</td>
<td>0.3</td>
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<tr>
<td>Increased ALP</td>
<td>13</td>
<td>0.5</td>
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<tr>
<td>Increased creatinine</td>
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<td>0.5</td>
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<tr>
<td>Increased triglycerides</td>
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<td>0.5</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>10</td>
<td>0.5</td>
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### 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>CABOMETYX (n=78)</th>
<th>Sunitinib (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td>CABOMETYX (n=78)</td>
<td>Sunitinib (n=72)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18%</td>
<td>33%</td>
</tr>
</tbody>
</table>

### Table 4. Adverse Reactions in 21% of Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX and Nivolumab (n=320)</th>
<th>Sunitinib (n=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td>CABOMETYX and Nivolumab (n=320)</td>
<td>Sunitinib (n=320)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>64%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
<td>61%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Hepatobiliary</strong></td>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>28%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Cough</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Palmar-Plantar Erythrodysesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>37%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestasis (<1%).
Table 5. Laboratory Values Worsening from Baselinea

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX</th>
<th>Nivolumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>120</td>
<td>26</td>
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<tr>
<td>Leukopenia</td>
<td>29</td>
<td>3</td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>120</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count</td>
<td>120</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>120</td>
<td>22</td>
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</tr>
<tr>
<td>Hyperkalemia</td>
<td>35</td>
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<tr>
<td>Hypocalcemia</td>
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<tr>
<td>Lymphopenia</td>
<td>67</td>
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<tr>
<td>Neutropenia</td>
<td>150</td>
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<tr>
<td>Platelet count</td>
<td>150</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed appetite</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Nervous System</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia</td>
<td>33</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 7. Laboratory Abnormalities Occurring in 25% of CABOMETYX-Treated Patients in CELESTIALa

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed appetite</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Nervous System</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia</td>
<td>33</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-311a

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed appetite</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Nervous System</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia</td>
<td>33</td>
<td>15</td>
</tr>
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</table>

Table 9. Laboratory Abnormalities Occurring in 25% of CABOMETYX-Treated Patients in COSMIC-311a

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed appetite</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Nervous System</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia</td>
<td>33</td>
<td>15</td>
</tr>
</tbody>
</table>

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 - 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 - 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years. Adverse reactions occurring in ≥5% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grades 3-4 adverse reactions occurring in ≥5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. The dose was reduced in 56% of patients receiving CABOMETYX; 22% of patients required a second dose reduction. The most frequent adverse reactions (≥5%) leading to dose reduction in ≥5% of patients were PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions occurring in ≥5% of patients receiving CABOMETYX were PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions requiring interruption in ≥5% of patients were PPE, diarrhea, fatigue, hypertension, and stomatitis. Adverse reactions occurring in ≥5% of patients receiving CABOMETYX were PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions requiring interruption in ≥5% of patients were PPE, diarrhea, fatigue, hypertension, and stomatitis. Adverse reactions occurring in ≥5% of patients receiving CABOMETYX were PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions requiring interruption in ≥5% of patients were PPE, diarrhea, fatigue, hypertension, and stomatitis.
In a pre- and postnatal study in rats, cabozantinib was administered at dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Advise pregnant women of the potential risk to a fetus. There are no available data in pregnant women. Based on findings from animal studies and its mechanism of action, CABOMETYX in pregnant women can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for new onset or worsening neurological function.

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, 51% 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.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the dosage of CABOMETYX in patients with severe hepatic impairment (Child-Pugh C). The safety and effectiveness of CABOMETYX in patients with severe renal impairment has not been established. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

8.7 Renal Impairment

In a pre- 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 outcome, 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).

8.8 Lactation

Increase in the frequency of bowel movements.

8.9 Effects of Other Drugs on CABOMETYX

6.7 7 3 7 6 1 6 5 4 3 2 1 0

Table 9. Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients in COSMIC-311

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX N=125</th>
<th>Placebo N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Smear Abnormalities</td>
<td>29 (23)</td>
<td>17 (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:
AUC = area under the curve

6.8 SAFETY

Hemorrhage: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

Bleed: 11.25

17  PATIENT COUNSELING INFORMATION

Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary emboli has been reported. Advise patients to contact their healthcare provider if 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 healthcare provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diabetes: Advise patients to notify their healthcare provider at the first signs of polyuria, polydipsia, loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable 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.

Recurrent posterior leukocerebral hemorrhage: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

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

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

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 07/2022

Distributed by Exelixis, Inc. Alameda, CA 94502

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Printed in USA 07/2022 CA-1121-5
**Phillips Evaluates Second-Line Therapy Options for R/R DLBCL**

**CASE**

- A 68-year-old man presented with fatigue, back pain, and lymphadenopathy.
- Medical history: hypertension, well controlled with medication
- Physical exam: left posterior cervical, 1.5-cm node; right anterior cervical, 2.5-cm node; left supraclavicular, 2.0-cm node
- PET-CT scan: multiple enlarged mesenteric and retroperitoneal nodes, largest measuring 5.3 × 3.1 cm
- Biopsy: diffuse large B-cell lymphoma (DLBCL), nongerminai center B cell-like
- Immunohistochemistry: positive for CD20, BCL6, BCL2 (50% of cells), MYC (> 90% of cells), Ki67 85%, MUM1; negative for CD10.
- Normal complete blood count but elevated lactate dehydrogenase levels
- Staging: stage III; International Prognostic Index (IPI) risk score, high-intermediate risk; nongerminai center
- ECOG performance status: 1
- Fluorescence in situ hybridization: negative for translocations involving MYC, BCL2, BCL6
- The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, prednisone) and back pain resolved.
- At the end of treatment, a PET scan showed a complete response with a Deauville score of 2.
- Eight months after completing therapy, the patient presented with fever, night sweats, and back pain.
- A palpable lymph node in left groin was discovered on physical examination.
- PET and CT scans showed new left inguinal lymph node, increase in size of residual node, as well as multiple metabolically active lesions in lymph nodes of the retroperitoneum, abdomen, and pelvis.
- Biopsy showed relapse of DLBCL.

**Tycel Phillips, MD**
Associate Clinical Professor  
Division of Lymphoma  
Department of Hematology & Hematopoietic Cell Transplantation  
City of Hope  
Duarte, CA

**Targeted Oncology™: What do the National Comprehensive Cancer Network (NCCN) guidelines recommend for the treatment of relapsed or refractory B-cell lymphomas?**

**PHILLIPS:** The most recently updated NCCN guidelines recommend that patients who relapse less than 12 months after chemotherapy go down a different pathway than our traditional course of salvage chemotherapy and [autologous stem cell transplant; ASCT]. The recommendation is to consider these patients for CAR [chimeric antigen receptor] T-cell therapy if the patients are eligible, able, and willing to go to a CAR T-cell therapy center.1

We have 2 CAR T-cell products in this space that will be options for patients with primary refractory DLBCL [diffuse large B-cell lymphoma] or early relapse DLBCL. We have axicabtagene ciloleucel [Yescarta], which has approval,2 and we have lisocabtagene maraleucel [liso-cel; Breyanzi], which recently gained approval for second-line therapy.3 For patients who aren’t candidates for CAR T-cell therapy, there are other regimens we can consider.1

**What studies have assessed the benefit of CAR T-cell therapy in primary refractory DLBCL?**

Several recent studies were designed to capture what we consider to be early relapse in primary refractory DLBCL, and they assessed the event-free survival benefit of CAR T-cell therapy vs the standard of care [SOC], which was salvage chemotherapy and ASCT. These studies were ZUMA-7 [NCT03391466], BELINDA [NCT03570892], and TRANSFORM [NCT03575351].

The median ages for all 3 studies were similar, [ranging from 58 to 60 years]. There were different patient populations in all 3 studies, which is something to [consider].4-6 ZUMA-7, which has the most mature data of the 3, did not allow any bridging chemotherapy, so these patients had to have disease stability sufficient to permit apheresis, manufacturing, and receipt of the study drug. There is always going to be some question about the patients enrolled on that study and how they compare [with] what we see in the real-world
setting. But the rate of CR [complete response] and progression-free survival [PFS] strongly favored CAR T-cell therapy vs the SOC therapy in this patient population. The BELINDA trial of tisagenlecleucel [tisa-cel; Kymriah] vs SOC did allow bridging therapy. However, there was no benefit to tisa-cel in this patient population. [It is worth noting that] tisa-cel is a bit more hampered than the other 2 CAR T-cell products [regarding] delays of manufacturing and delivering this product to patients. I don’t think anybody can say with certainty how that may have contributed to the outcomes in this study, but of the 3 studies, this is the only one that had a negative outcome. It showed no substantial benefit to CAR T-cell therapy.

Compared with ZUMA-7, the TRANSFORM trial [of liso-cel vs SOC] was smaller [and the data are less mature], but this study did show significant benefits to overall response rate [ORR], CR rate, and PFS for CAR T-cell therapy. The results were recently published in Lancet and led to [the] approval of this agent in the second-line setting.

[As a result of] these studies, we have 2 agents that have been approved for second-line treatment of primary refractory or early relapse DLBCL. We’ll have to consider how this will change our clinical practice, because CAR T-cell therapy is still limited by access for most patients, and there’s still a delay with manufacturing.

**CASE UPDATE**

The patient was referred to the nearest transplant and cellular therapy center for evaluation but ultimately opted not to pursue CAR T-cell therapy.

What options should be considered for such a patient at this juncture?

At this point, we face the more common salvage options. The preferred regimens are GemOx [gemcitabine (Gemzar) and oxaliplatin (Eloxatin)] with or without rituximab, polatuzumab vedotin-piiq [Polivy] with or without bendamustine [Bendeka] and rituximab, and tafasitamab-cxix [Monjuvi] plus lenalidomide [Revlimid]. These options are for patients who are not considered candidates for ASCT. The patient we are discussing is likely not a candidate for ASCT, because he [is unlikely to] respond to chemoimmunotherapy and [achieve] remission.

GemOx is something we’re all very familiar with, and I give it every 2 or 3 weeks. Polatuzumab vedotin [with or without] bendamustine, rituximab, [or both] is approved to treat large cell lymphoma [after more] than 2 lines of therapy. Polatuzumab is an antibody-drug conjugate that targets CD79b and has monomethyl auristatin E [MMAE] conjugated to it. MMAE is a common payload on a multitude of antibodies we use. Tafasitamab is a CD19-targeted antibody, and lenalidomide is an immunomodulatory agent. This combination is approved to treat adults with relapsed or refractory DLBCL who are not eligible for ASCT.

A key footnote is that we have very little data about whether tafasitamab-cxix, loncastuximab tesirine-ipyl [Zynlonta], or any other CD19-directed therapy would have a negative effect on the efficacy of subsequent anti-CD19 CAR T-cell therapy. We’ll get more real-world data about these situations, even though most physicians prefer polatuzumab-piiq without bendamustine as a bridge to CAR T-cell therapy. [In light of] the adverse event [AE] profile of polatuzumab, the role of these other therapies and their impact on CAR T-cell therapy is something we’ll need to investigate. There are some preliminary data showing that loncastuximab has no real impact on the efficacy of CAR T-cell therapy, but unfortunately, we don’t have as much data for tafasitamab.

**POLLING QUESTION**

At a live virtual event Phillips asked participants, "What are you most likely to recommend for this patient with primary refractory DLBCL who has declined CAR T-cell therapy?"

<table>
<thead>
<tr>
<th>Option</th>
<th>Vote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polatuzumab/bendamustine/rituximab</td>
<td>57%</td>
</tr>
<tr>
<td>GemOx plus rituximab</td>
<td>29%</td>
</tr>
<tr>
<td>Tafasitamab/lenalidomide</td>
<td>14%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
</tr>
</tbody>
</table>

Total votes: 7

What data support the various recommended second-line therapies for transplant-eligible DLBCL?

A [retrospective] study of R-GemOx [GemOx plus rituximab] looked at 196 patients with a median age of 72 years and a median of 1 prior line of therapy. A little over half of these patients [57%] were primary refractory. After a median follow-up of 22 months, the [ORR] was 38%, the CR rate was 33%, the median PFS was 5 months, and the median overall survival [OS] was 10 months.

The combination of polatuzumab vedotin plus bendamustine and rituximab [BR] was compared with BR alone in a randomized study [NCT02257567], with 48 patients in each arm. [In the experimental arm], the median age was 67 years and patients had received a median of 2 prior lines of therapy. Three-fourths of these patients were primary refractory. After a median follow-up of 27 months, the [ORR] was 45%, the CR rate was 40%, the median PFS was 9.5 months, and the median OS was 12.4 months.

The combination of tafasitamab plus lenalidomide was examined in the L-MIND study [NCT02399085]. [This study involved] 81 patients, with a median age of 72 years.
and a median of 2 prior lines of therapy. [A total of] 44% [of patients] would be considered refractory [to the last prior therapy]. After a median follow-up of 42.7 months, the [ORR] was 57.5%, the CR rate was 40.0%, the median PFS was 11.6 months, and the median OS was 33.5 months.\textsuperscript{12} It was [based on] these results that this combination was approved.\textsuperscript{9}

How was the L-MIND trial designed? What additional data did it yield?

In the L-MIND trial, tafasitamab was given at a dosage of 12 mg/kg on days 1, 8, 15, and 22 on a 28-day cycle. During the first cycle, there was an additional loading dose given on day 4. Oral lenalidomide was given at a dosage of 25 mg daily on days 1 through 21 of a 28-day cycle. Beginning with cycle 4, tafasitamab was given on days 1 and 15. After a total of 12 cycles, lenalidomide was discontinued and patients could continue on single-agent tafasitamab. The study did have a modification of its eligibility criteria such that it excluded refractory patients while the study was ongoing, so there were some refractory patients [enrolled in the study], but [most] would be considered relapsed per our current definition.\textsuperscript{13,14}

At baseline, patients’ [International Prognostic Index] score was evenly split between 0 to 2 and 3 to 5. Most patients [75%] had stage III or IV disease. Approximately half the patients [56%] had elevated [lactate dehydrogenase]. Additionally, 19% of the patients were considered to be primary refractory, 44% were refractory to the last prior therapy, and 11% had received a prior stem cell transplant. Finally, the distribution of subtypes germinal B-cell–like [GCB], non-GCB, and unclassified or unknown was [10%, 25%, and 65%], respectively.\textsuperscript{12,13}

After a little more than 35 months of follow-up, the CR rate was 40.0% and the partial response [PR] rate was 17.5%. Additionally, 16.3% of the patients had stable disease and another 16.3% had progressive disease. The ORR, combining the rates of CR and PR, was 57.5% and the median duration of response [DOR] was 43.9 months.\textsuperscript{12,13}

Not surprisingly, the best DOR was seen in patients who achieved a CR [median DOR, not reached (NR); 95% CI, 43.9-NR]. Patients who achieved a PR had a very low DOR of 5.6 months [95% CI, 2.2-NR]. When these 2 groups were combined, the median DOR was 43.9 months [95% CI, 26.1-NR]. The median time to response was 2.1 months [range, 1.7–34.7] and the median time to CR was 6.8 months [range, 1.7–46.3].\textsuperscript{12} This [drug combination acts] a little more slowly than other cytotoxic agents, for which best responses are typically seen very early. Because of the mechanism of action of this combination, a [somewhat longer time is required] to get patients’ disease under control and to achieve the best response.

After a median of 33.9 months of follow-up, the median PFS was 11.6 months. The percentage of patients still in remission was 50% at 12 months and 46% at 18 months. After a median of 42.7 months of follow-up, the median OS was 33.5 months. The percentage of patients surviving was 74% at 12 months and 64% at 18 months. [In analyses of PFS and OS, as in the analysis of DOR], patients who achieved a CR had better outcomes [PFS, NR; 95% CI, 45.7-NR; OS, NR; 95% CI, 45.7-NR] [than did patients who achieved a PR (PFS, 7.4 months; 95% CI, 5.3-NR; OS, 22.5 months; 95% CI, 8.6-NR) or stable disease].\textsuperscript{12}

One key caveat that came from the L-MIND study was that the earlier you implement this treatment, the better the outcomes seem to be. Among patients who had received only 1 prior line of therapy, there was a higher percentage of patients with CR and PR, a longer duration of response, and higher rates of PFS and OS relative to the group of patients who had received 2 or more prior lines of therapy [Figure\textsuperscript{15}]. This is something to take into consideration, especially for frail patients or those who are unfit and unable to get to CAR T-cell therapy or ASCT.

The most common hematological AEs were neutropenia, anemia, and thrombocytopenia [of grades 1 to 4. These AEs affected 49%, 34%, and 31% of patients, respectively]. Other hematological AEs were leukopenia, febrile neutropenia, lymphopenia, and agranulocytosis. There were no grade 5 hematological AEs.\textsuperscript{13}

The most common nonhematological AEs were rash, diarrhea, asthenia, cough, fever, peripheral edema, upper respiratory tract infection, and anorexia.\textsuperscript{13} Most of the AEs, including the hematological AEs, were consistent with what we see with single-agent lenalidomide.

Serious AEs occurred in 51% of the patients. Those thought to be treatment-related affected only 19%, as assessed by the investigators, and 12% of the patients had discontinuation of therapy [because of] AEs. There were 7 patients with AEs of special interest: [3 with tumor flare, 1 with basal cell carcinoma, and 3 with grade 3 allergic dermatitis]. Treatment-emergent AEs leading to death occurred in 13% of the patients [4 of 30]. One or more dose reductions of lenalidomide were required for 45.7% of the patients. Most patients [77.5%] were able to receive a lenalidomide dose of at least 20 mg daily over the duration of treatment, which is probably in line with the dosage most of us use.\textsuperscript{13,15,16}

Upon discontinuation of lenalidomide, patients were able to continue treatment with single-agent tafasitamab. The AE profile of the combination was compared with that of single-agent tafasitamab, and the data showed that the incidence and severity of treatment-emergent AEs decreased during the tafasitamab monotherapy period. This is especially true of some of the AEs that are more consistently seen with lenalidomide. [When lenalidomide was discontinued], there was a
complete resolution of thrombocytopenia and a reduction in the incidence and severity of neutropenia, anemia, diarrhea, asthenia, rash, and peripheral edema.**

REFERENCES

6. Kamdar M, Solomon SR, Arnason JE, et al. Lisocabtagene maraleucel (liso-cell), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, versus standard of care (SOC) with salvage chemotherapy (CT) followed by autologous stem cell transplantation (ASCT) as second-line (2L) treatment in patients (Pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL): results from the randomized phase 3 TRANSFORM study. *Blood.* 2021;138(suppl 1):91. doi:10.1182/blood-2021-147913
doi:10.1016/S0140-6736(22)00662-6

**FIGURE.** Outcomes by Prior Treatment Lines in the L-MIND Trial (at minimum 35 months follow-up)**

![Outcomes by Prior Treatment Lines in the L-MIND Trial](image-url)
dMMR Recurrent or Advanced Endometrial Cancer
ILLUMINATED

INDICATION
JEMPERLI is indicated for the treatment of adult patients with mismatch repair-deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue and can occur at any time during or after treatment with a PD-1/PD-L1–blocking antibody, including JEMPERLI.
- Monitor closely for signs and symptoms of immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. For suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Based on the severity of the adverse reaction, withhold or permanently discontinue JEMPERLI. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to ≤Grade 1. Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Immune-Mediated Pneumonitis

- JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Pneumonitis occurred in 1.4% (7/515) of patients, including Grade 2 (1.2%) and Grade 3 (0.2%) pneumonitis.

Immune-Mediated Colitis

- Colitis occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis. In such cases, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis

- JEMPERLI can cause immune-mediated hepatitis, which can be fatal. Grade 3 hepatitis occurred in 0.2% (1/515) of patients.

Immune-Mediated Endocrinopathies

- Adrenal Insufficiency
  - Adrenal insufficiency occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Hypophysitis
  - JEMPERLI can cause immune-mediated hypophysitis. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Nephritis with Renal Dysfunction

- JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis occurred in 0.4% (2/515) of patients; both were Grade 2. Hypothyroidism occurred in 7.2% (37/515) of patients, all of which were Grade 2. Hyperthyroidism occurred in 1.9% (10/515) of patients, including Grade 2 (1.7%) and Grade 3 (0.2%). Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Dermatologic Adverse Reactions

- Rash
  - Rash occurred in 8.9% (46/515) of patients, including Grade 2 (3.5%) and Grade 3 (0.6%). Rash can be fatal. For Grade 2 or higher rash, withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Gastrointestinal Adverse Reactions

- Pancreatitis
  - Pancreatitis occurred in 0.8% (4/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.2%). Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Ocular Adverse Reactions

- Uveitis
  - Uveitis occurred in 0.6% (3/515) of patients, including Grade 2 (0.4%) and Grade 3 (0.2%). Monitor patients for increased intraocular pressure or other signs and symptoms of ocular toxicity. Initiate treatment with topical medications as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Other Immune-Mediated Adverse Reactions

- Adverse reactions occurred in <1% of the 515 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases occurred in <1% of patients, all of which were Grade 2. Hyperthyroidism occurred in 1.9% (10/515) of patients, including Grade 2 (1.7%) and Grade 3 (0.2%). Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Learn more about JEMPERLI at JEMPERLIHCP.COM
JEMPERLI has demonstrated clinically meaningful efficacy\textsuperscript{1,2}

**Primary efficacy analysis (n=71)**

- **42.3%** ORR\textsuperscript{1} 95% CI (30.6, 54.6)
- **12.7%** of patients experienced complete response\textsuperscript{1}

**Updated efficacy analysis (n=103)**

- **44.7%** ORR\textsuperscript{1} 95% CI (34.9, 54.8)
- **10.7%** of patients experienced complete response\textsuperscript{2}

\begin{itemize}
  \item In the primary analysis, the median duration of response was not reached with a median follow-up time of 14.1 months.\textsuperscript{1}\textsuperscript{1}
  \item The updated analysis showed a median duration of response of 34.7 months with a median follow-up of 20.4 months\textsuperscript{2}\textsuperscript{2}
\end{itemize}

The efficacy of JEMPERLI was investigated in a global, multicenter, multiple cohort, open-label study of 71 patients with recurrent or advanced dMMR endometrial cancer who had progressed on or after treatment with a platinum-containing regimen. Patients received JEMPERLI 500 mg via intravenous infusion every 3 weeks for 4 doses followed by 1000 mg every 6 weeks until disease progression or unacceptable toxicity. An updated efficacy analysis for JEMPERLI included 103 patients using the same study criteria.\textsuperscript{1}

\textsuperscript{1}As measured from time of first response.\textsuperscript{1}
\textsuperscript{2}Median follow-up time is a post hoc analysis of time since initial response.\textsuperscript{2}

JEMPERLI has an established safety profile\textsuperscript{1,2}

- 4.8% of patients permanently discontinued treatment due to adverse reactions
- The most common adverse reactions (≥20%) were fatigue/asthenia, nausea, diarrhea, anemia, and constipation
- Safety data from the updated analysis were consistent with the established safety profile

\textsuperscript{1}As measured from time of first response.\textsuperscript{1}
\textsuperscript{2}Median follow-up time is a post hoc analysis of time since initial response.\textsuperscript{2}

**Complications of Allogeneic HSCT**

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after treatment with a PD-1/PD-L1–blocking antibody, which may occur despite intervening therapy. Monitor patients closely for transplant-related complications and intervene promptly.

**Embryo-Fetal Toxicity and Lactation**

- Based on its mechanism of action, JEMPERLI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after their last dose. Because of the potential for serious adverse reactions from JEMPERLI in a breastfed child, advise women not to breastfeed during treatment with JEMPERLI and for 4 months after their last dose.

**Common Adverse Reactions**

The most common adverse reactions (≥20%) in patients with dMMR EC were fatigue/asthenia, nausea, diarrhea, anemia, and constipation. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, decreased leukocytes, decreased albumin, increased creatinine, increased alkaline phosphatase, and increased alanine aminotransferase.

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

References:
1. JEMPERLI. Prescribing Information. GlaxoSmithKline; 2022.
2. Data on file, GlaxoSmithKline.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred in <1% of the 515 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
  \begin{itemize}
    \item **Nervous System**: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy
    \item **Cardiac/Vascular**: Myocarditis, pericarditis, vasculitis
    \item **Ocular**: Uveitis, iritis, other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur
    \item **Gastrointestinal**: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis
    \item **Musculoskeletal and Connective Tissue**: Myositis/myositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
    \item **Endocrine**: Hypoparathyroidism
    \item **Other (Hematologic/Immune)**: Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection
  \end{itemize}

Infusion-Related Reactions

- Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction.

Infusion-Related Reactions

- Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction.
Jemapritil (dostarlabin-glx) injection, for intravenous use

The following is a brief summary only; see full prescribing information for complete product information available at www.JEMPERLICHP.com.

1 INDICATIONS AND USAGE
JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen (see Dosage and Administration [2.3] of full prescribing information).

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe and Fatal Immune-Mediated Adverse Reactions
JEMPERLI is a monoclonal antibody that belongs to a class of drugs that bind to either PD-1 or PD-L1 and may cause immune dysregulation, which can manifest as severe and fatal immune-mediated reactions.

Important immune-mediated adverse reactions listed in WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1–blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1–blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1–blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests 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 JEMPERLI depending on severity (see Dosage and Administration [2.3] of full prescribing information). In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., enocrinopathies, dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis
JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with either PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 1.4% (7/515) of patients receiving JEMPERLI, including Grade 2 (1.2%) and Grade 3 (0.2%) pneumonitis. Pneumonitis led to discontinuation of JEMPERLI in 0.6% patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 86% of the 7 patients. Two patients reinitiated JEMPERLI after symptom improvement; of these, 1 patient had recurrence of pneumonitis.

Immune-Mediated Colitis

Immune-mediated colitis occurred in 1.4% (7/515) of patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Colitis led to discontinuation of JEMPERLI in 1 (0.2%) patient.

Systemic corticosteroids were required in 29% (2/7) of patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 3 patients in whom JEMPERLI was withheld for colitis, all reinstituted treatment with JEMPERLI.

Immune-Mediated Hepatitis
JEMPERLI can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 0.2% (1/515) of patients receiving JEMPERLI, which was Grade 3. Systemic corticosteroids were required and the event resolved.

Immune-Mediated Endocrinopathies
Adrenal Insufficiency: JEMPERLI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity (see Dosage and Administration [2.3] of full prescribing information).

Adrenal insufficiency occurred in 1.4% (7/515) patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%). Adrenal insufficiency resulted in discontinuation in 1 (0.2%) patient and resolved in 29% of the 7 patients.

Hypophysitis: JEMPERLI 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 hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity (see Dosage and Administration [2.3] of full prescribing information).

Thyroid Disorders: JEMPERLI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathies. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity (see Dosage and Administration [2.3] of full prescribing information).

Hyperthyroidism: Hyperthyroidism occurred in 7.2% (37/515) of patients receiving JEMPERLI, all of which were Grade 1. Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 35% of the 37 patients. Systemic corticosteroids were not required for any of the 37 patients with hyperthyroidism.

Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis: JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity (see Dosage and Administration [2.3] of full prescribing information).

Immune-Mediated Nephritis with Renal Dystunction
JEMPERLI can cause immune-mediated nephritis, which can be fatal. Pneumonitis led to discontinuation of JEMPERLI in 3 (0.6%) patients receiving JEMPERLI. Adverse reactions that may be associated with these conditions are described elsewhere in the WARNINGS AND PRECAUTIONS section.

Immune-Mediated Dermatologic Adverse Reactions
JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity (see Dosage and Administration [2.3] of full prescribing information).

Other Immune-Mediated Adverse Reactions
The following clinically significant immune-
can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions [see Warnings and Precautions (5.1)]
- Infusion-related reactions [see Warnings and Precautions (5.2)].

6.1 Clinical Trials Experience

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

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to JEMPERLI as a single-agent in 515 patients with advanced or recurrent solid tumors in the non-randomized, open-label, multicohort GARNET trial that enrolled 290 patients with endometrial cancer and 225 patients with other solid tumors. JEMPERLI was administered intravenously at doses of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until disease progression or unacceptable toxicity. Among the 515 patients, 42% were exposed for ≥24 weeks and 26% were exposed for >48 weeks.

Mismatch Repair Deficient (dMMR) Endometrial Cancer

The safety of JEMPERLI was evaluated in GARNET in 104 patients with advanced or recurrent dMMR EC who received at least 1 dose of JEMPERLI [see Clinical Studies (14.1) of full prescribing information]. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until intravenous infusion until disease progression or unacceptable toxicity. Patients with autologous disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Among patients receiving JEMPERLI, 47% were exposed for 6 months or longer and 20% were exposed for >1 year.

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions in >2% of patients included sepsis (2.9%), acute kidney injury (2.9%), urinary tract infection (2.9%), abdominal pain (2.9%), and pyrexia (2.9%).

JEMPERLI was permanently discontinued due to adverse reactions in 5 (4.8%) patients, including increased transaminases, sepsis, bronchitis, and pneumonitis. Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in ≥1% of patients who received JEMPERLI were anemia, diarrhea, increased lipase, and pyrexia.

The most common adverse reactions (≥20%) were fatigue, asthenia, nausea, diarrhea, anemia, and constipation. The most common Grade 3 or 4 adverse reactions (≥2%) were anemia and increased transaminases. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, decreased leukocytes, decreased albumin, increased creatinine, increased alanine aminotransferase and increased alanine aminotransferase.

Table 1 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR EC on JEMPERLI in GARNET.

### Table 1. Adverse Reactions (≥10%) in Patients with dMMR Endometrial Cancer Who Received JEMPERLI in GARNET

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades %</th>
<th>Grade 3 or 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>General and administration site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13</td>
<td>1.9</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cont)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 5.2 Infusion-Related Reactions

Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1 blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction [see Dosage and Administration (2.3) of full prescribing information].

### 5.3 Complications of Allogeneic H SCT

Fatal and other serious complications can occur in patients who receive donor hematopoietic stem cell transplantation (H SCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-vs-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic H SCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic H SCT.

### 5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, JEMPERLI...
the developing fetus. Advise women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data: Animal reproduction studies have not been conducted with JEMPERLI to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering JEMPERLI during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to dostarlimab-gxly may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation
Risk Summary
There is no information regarding the presence of dostarlimab-gxly in human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 4 months after the last dose of JEMPERLI.

8.3 Females and Males of Reproductive Potential
JEMPERLI can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

pregnancy
Verify pregnancy status in females of reproductive potential [see Use in Specific Populations (8.1)].

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

8.4 Pediatric Use
The safety and efficacy of JEMPERLI have not been established in pediatric patients.

8.5 Geriatric Use
Of the 515 patients treated with JEMPERLI, 51% were younger than 65 years, 37% were aged 65 through 75 years, and 12% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

immune-mediated adverse reactions
Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid or other treatment and interruption or discontinuation of JEMPERLI. These reactions may include:

• Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1)].
• Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see Warnings and Precautions (5.1)].
• Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding [see Warnings and Precautions (5.1)].
• Immune-mediated endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus [see Warnings and Precautions (5.1)].
• Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see Warnings and Precautions (5.1)].
• Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS, TEN, or DRESS [see Warnings and Precautions (5.1)].
• Other immune-mediated adverse reactions:
  • Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms [see Warnings and Precautions (5.1)].
  • Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection [see Warnings and Precautions (5.1)].

Infusion-related Reactions
• Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.2)].

Complications of Allogeneic HCT
• Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity
• Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1), 8.3].
• Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose [see Warnings and Precautions (5.4), Use in Specific Populations (8.1), 8.3].
• Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose [see Warnings and Precautions (5.4), Use in Specific Populations (8.1), 8.3].

Lactation
• Advise women not to breastfeed during treatment with JEMPERLI and for 4 months after the last dose [see Use in Specific Populations (8.2)].

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Tannir Discusses Combination Therapy Data in Advanced RCC

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. The patient received pembrolizumab (Keytruda)/lenvatinib (Lenvima) as part of a clinical trial.

What was the efficacy seen in patients in this trial?

In the Kaplan-Meier curves for PFS in the CLEAR study...I think it’s important to note that the 2 experimental arms, lenvatinib plus pembrolizumab and lenvatinib plus everolimus, in terms of PFS, showed a significant difference compared with sunitinib. The median PFS with lenvatinib/pembrolizumab was 23.9 months vs 9.2 months with sunitinib, and the median PFS for lenvatinib/everolimus was 14.7 months.

The hazard ratio for the difference for PFS between lenvatinib/pembrolizumab and sunitinib was 0.39 [95% CI, 0.32-0.49; P < .001]. That corresponds to a 61% reduction in the risk of progression or death in favor of lenvatinib/pembrolizumab. The hazard ratio for lenvatinib/everolimus vs sunitinib was 0.65, which corresponds to a 35% reduction in the risk of death or progression [95% CI, 0.53-0.80; P < .001].

The prespecified analysis of adverse prognostic features included bone metastases, liver metastases, PD-L1 expression, prior nephrectomy, and sarcomatoid component. For all those covariables, the lenvatinib/pembrolizumab regimen performed better than sunitinib.

The difference in OS between lenvatinib/pembrolizumab vs sunitinib was significant, with a hazard ratio of 0.66 that corresponds to a reduction of mortality or death by 34% [95% CI, 0.49-0.88; P = .005].

Targeted Oncology™: Can you discuss the design of the phase 3 CLEAR study (NCT02811861) in advanced clear cell carcinoma (RCC)?

TANNIR: The design was frontline lenvatinib plus pembrolizumab vs lenvatinib plus everolimus [Afinitor] vs sunitinib [Sutent]. This was a 3-arm study. For this phase 3 trial of first-line therapy in advanced clear RCC, the eligibility criteria were for treatment-naive patients with advanced clear cell RCC, Karnofsky performance status of 70% or better, measurable disease, and adequate organ function.

For the CLEAR study, the 2 strata were geographic region: Western Europe and North America vs the rest of the world, and MSKCC [Memorial Sloan Kettering Cancer Center] risk category: favorable, intermediate, or poor risk. In this trial, for risk stratification, they use the MSKCC; but for other trials [in this setting], the IMDC [International Metastatic RCC Database Consortium] risk model was used.

Patients were [randomly assigned] fairly, 1:1:1, to receive either lenvatinib plus pembrolizumab or lenvatinib plus everolimus or sunitinib. The primary end point was progression-free survival (PFS) by independent radiology committee or panel, using RECIST version 1.1. Secondary end points were overall survival (OS), objective response rate (ORR) by independent radiology committee using RECIST version 1.1, safety, and health-related quality-of-life outcomes. There were also key exploratory end points: duration of response and biomarkers.
The confirmed ORR with lenvatinib/pembrolizumab in this CLEAR study was 71% compared with 36.1% with sunitinib and 53.5% with lenvatinib/everolimus.¹ When you look at complete response (CR) rate, it was an impressive 16.1% with lenvatinib/pembrolizumab vs 9.8% with lenvatinib/everolimus vs 4.2% with sunitinib.

When you look at data from any phase 3 trial, you look at what the progressive disease (PD) rate is for a treatment regimen. PD with lenvatinib/pembrolizumab was very low. I think we all would like to see that PD rate as low as possible, and with lenvatinib/pembrolizumab the PD rate was 5.4% and with sunitinib it was 14.0%. Even with lenvatinib/everolimus, the PD rate was 7.3%.

The median duration of response was an exploratory end point in the CLEAR study. The median duration of response was 25.8 months with lenvatinib/pembrolizumab vs 16.6 months with lenvatinib/everolimus vs 14.6 months with sunitinib. I think it’s important to also highlight that among patients who experienced a CR with lenvatinib/pembrolizumab in the intent-to-treat population, almost 80% of patients maintained a CR at 24 months and almost three-fourths maintained a CR at 3 years.⁴

How did patients respond to treatment in terms of toxicity?

Looking at treatment exposure, safety, and discontinuation in the phase 3 CLEAR study, median duration of treatment was 17 months with lenvatinib/pembrolizumab vs 11 months with lenvatinib/everolimus vs 7.8 months with sunitinib. Universally, just about every patient on this trial had any-grade treatment-emergent adverse events [TEAEs]; almost all patients developed 1 TEAE or more.

But if you look at grade 3 or 4 TEAEs, 82% of patients treated with lenvatinib/pembrolizumab had grade 3 or 4. It was almost identical with lenvatinib/everolimus, and it was a little lower with sunitinib, at 71.8%. Patients with any AE leading to dose reduction of either lenvatinib or sunitinib was 68.8% in the lenvatinib/pembrolizumab arm vs 73.2% with lenvatinib/everolimus vs 50.3% with sunitinib.

It is important, in addition to AEs leading to reduction or interruption, to look at discontinuation of therapy. When you look at the lenvatinib/pembrolizumab regimen, almost a quarter of the patients had to discontinue lenvatinib in the lenvatinib/pembrolizumab arm, 22% in the lenvatinib/everolimus arm, and 14.4% with sunitinib.

When you look at discontinuation of either pembrolizumab or everolimus in the combination arm, with the lenvatinib/pembrolizumab regimen, 28.7% discontinued pembrolizumab and 24.8% discontinued everolimus in the lenvatinib/everolimus arm, so a little over a quarter of the patients discontinued pembrolizumab.¹ But [13.4% discontinued] both lenvatinib/pembrolizumab, and 18.9% discontinued both lenvatinib/everolimus. Looking at TEAEs with frequency of 20% or more for lenvatinib/pembrolizumab vs sunitinib...diarrhea was on top in terms of garnering the highest number of any-grade AEs, closely followed by hypertension, then stomatitis, hypothyroidism, fatigue, hand-foot skin reaction, decreased appetite, nausea, dysgeusia, asthenia, rash, and dysphonia.

I think it’s important to note that hypertension, grade 3 and 4, with lenvatinib/pembrolizumab was 25.3%; so about a quarter of the patients treated with lenvatinib/pembrolizumab had grade 3 or 4 hypertension. With sunitinib, 17.9% had grade 3 or 4 hypertension.

In the CLEAR study, the recommended starting dose of lenvatinib was 20 mg daily, and pembrolizumab was 200 mg every 3 weeks, up to 2 years.⁵ ⁶ Many of us now have also given pembrolizumab 400 mg every 6 weeks, which would be more convenient, but in the CLEAR study the dosing schedule was 200 mg every 3 weeks.

Pembrolizumab was discontinued after 2 years, and lenvatinib was continued until progressive disease or toxicity.⁵ ⁶ For those of you who have used the lenvatinib/pembrolizumab regimen, the lenvatinib capsules come in 4 mg and 10 mg. The starting dose [is] 20 mg and the first reduction is to 14 mg, in case of toxicity; for the second reduction, you go down to 10 mg, and then you go down to the third reduction, which is 8 mg. This is based on the package insert for prescribing information, as well as the dose modifications from the trial.

In practice, if I have a patient on lenvatinib/pembrolizumab and they have responded, but they had AEs and they did not tolerate the 8 mg, I go down to 4 mg. Many of my colleagues [do this] also.

Can you discuss the CheckMate 9ER trial (NCT03141177) for advanced RCC?

The phase 3 trial CheckMate 9ER investigated the regimen of nivolumab/cabozantinib [Opdivo/Cabometyx] that was approved in January 2021.⁷ ⁸ The study had similar inclusion criteria to what we heard before, but unlike the CLEAR study, the IMDC grouping was selected for inclusion, for eligibility criteria. This was a 2-arm study with cabozantinib 40 mg daily and nivolumab 240 mg every 2 weeks [vs sunitinib].

Many of us rarely give nivolumab every 2 weeks at 240 mg—we give 480 mg every 4 weeks—but in the CheckMate 9ER trial, this was the dosing schedule.⁷ The primary end point was PFS by blinded independent radiology review. Secondary end points included OS, ORR, and safety. The stratification factors were IMDC risk scoring—many of the BMS [Bristol Myers Squibb] trials used PD-L1 expression as one of the stratification factors—and geographic region.
The median PFS with a combination of nivolumab/cabozantinib was 16.6 months, which was double the median PFS with sunitinib of 8.3 months. This had a hazard ratio of 0.51, which means a 49% reduction of death or progress of disease, and this had a significant P value [95% CI, 0.41–0.64; P < .0001].

As we saw with the CLEAR study, in the CheckMate 9ER study, [regarding] PFS by subgroup with blinded independent central radiology review compared with sunitinib, the combination of nivolumab/cabozantinib fared better vis-à-vis the covariables that they looked at.¹ ²

Looking at ORR and best overall response in the primary analysis, with 18-month median follow-up, there was an 8% CR rate with nivolumab/cabozantinib vs 4.6% CR rate with sunitinib.³ And that important PD rate, 5.6 months—low PD rate—with nivolumab/cabozantinib vs about 14%. That was the same PD rate in the CLEAR study with sunitinib. Median time to response: 2.8 months with the nivolumab/cabozantinib combination vs 4.2 months with sunitinib. These are similar data to what we observed in CheckMate 214 [NCT02231749] with nivolumab/ipilimumab [Yervoy] vs sunitinib.⁴ Median duration of response was 20.2 months with the nivolumab/cabozantinib combination vs 11.5 months with sunitinib.

What are the most recent findings for the patients in CheckMate 9ER?
The follow-up was presented in San Francisco at the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium—a median follow-up of the study of 33 months compared with 18 months for the primary analysis.⁵ The median PFS was exactly the same, 16.6 months vs 8.3 months, and the hazard ratio for the difference between the 2 arms was 0.56 at the follow-up. Again, 95% confidence intervals are very tight, 0.46 to 0.68.

The latest follow-up for the study showed nivolumab/cabozantinib [vs] sunitinib was 70% vs 60% probability of OS at 24 months; so at 2 years, [with a] 10 percentage point difference in OS, probability is in favor of the combination. The median OS for the combination of nivolumab/cabozantinib was 37.7 months vs 34.3 months with sunitinib. This had a hazard ratio of 0.70, so that’s a 30% reduction in the risk of death in favor of nivolumab plus cabozantinib [95% CI, 0.55–0.90].

The ORR with nivolumab/cabozantinib was 55.7%, basically identical to the prior analysis, vs 28.4% with sunitinib, very similar to the 27.1% in the primary analysis. But the CR rate with nivolumab/cabozantinib increased from 8% to 12.4% with further follow-up, and the CR rate with sunitinib was 5.2%. Median duration of response was about 2 years—23.1 months with the nivolumab/cabozantinib combination vs 15.1 months with sunitinib.

How did patients with RCC respond to the AEs of nivolumab/cabozantinib?
Safety is important to look at. Median duration of therapy was 14.3 months with nivolumab/cabozantinib vs 9.2 months with sunitinib.⁶ [Of] patients with at least 1 dose reduction—whether it’s cabozantinib or sunitinib—56.3% had to reduce the dose.

We know that for nivolumab, we do not reduce the dose; we just skip or delay the administration of nivolumab. So the dose reduction is only for the tyrosine kinase inhibitor. There were 51.6% of patients on the sunitinib arm who had to dose reduce from 15 mg down to 7.5 mg. Discontinuation for any reason, not just toxicity, was 44.4% with nivolumab/cabozantinib vs 71.3% with sunitinib; the reason for higher discontinuation is because of a higher PD rate with sunitinib.

But when you look at treatment discontinuation due to toxicity, or any-grade treatment-related AEs, around 15% of patients on nivolumab/cabozantinib would discontinue therapy. Because of treatment-related AEs, discontinuation of nivolumab only was 5.6%, cabozantinib only was 6.6%, and both nivolumab and cabozantinib were 3.1%.

Now with the updated data with median follow-up of 33 months, discontinuation at 23.5-month follow-up was 9.7% for nivolumab only vs 7.2% for cabozantinib only vs 6.6% for the combination.⁷ For any-grade [AEs], there were 97%—almost universal as we saw with the other trial—AEs in both arms.⁸ For grades 3, 4, and higher, 65% of patients had grade 3 or 4 with the combination of nivolumab/cabozantinib vs 54% with sunitinib.

[The most common any-grade AE was] diarrhea, similar to what we saw in the CLEAR study.⁹ Then hand-foot skin reaction comes [in at] number 2, then hypertension.¹⁰

FOR FULL LIST OF REFERENCES, VISIT TARGETEDONC.COM

### Strategic Alliance Partnership

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Roundtable Discussion: Comparing Triplet vs Quadruplet Regimens as Maintenance for NDMM

CASE SUMMARY

A 54-year-old woman received a diagnosis of Revised International Staging System stage II multiple myeloma.

<table>
<thead>
<tr>
<th>Laboratory results</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>7.0 g/dL</td>
</tr>
<tr>
<td>β₂-Microglobulin</td>
<td>6 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2 g/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>11.3 mg/dL</td>
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<tr>
<td>Lactate dehydrogenase</td>
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<tr>
<td>Creatinine clearance</td>
<td>45 mL/min</td>
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<tr>
<td>Bone marrow</td>
<td>22% clonal plasma cells</td>
</tr>
<tr>
<td>Serum free κ light chains</td>
<td>24 mg/dL</td>
</tr>
<tr>
<td>Serum monoclonal protein</td>
<td>5 g/dL</td>
</tr>
</tbody>
</table>

Fluorescence in situ hybridization and karyotyping showed no cytogenetic abnormalities. Her ECOG performance status was 1. PET-CT scan showed multiple bone lesions in the vertebrae. There was no extramedullary disease. She received a diagnosis of IgG-κ multiple myeloma and was told she was transplant eligible.

DISCUSSION QUESTIONS

• What are the available triplet regimen and quadruplet regimen options for patients with transplant-eligible newly diagnosed multiple myeloma (NDMM)?
• How do you decide between quadruplet and triplet regimens?
  ◦ What factors impact the use of quadruplet vs triplet?
• For a patient who is eligible for transplantation, do you initiate treatment with a quadruplet or triplet regimen?
• In your experience, how do responses compare between the 2 approaches?

BRAUNSTEIN: In multiple myeloma, if you ask a panel of experts a question, you’ll get 10 different answers. There are various regimens; what are some of the most common ones that you’ve adopted in your practice?

WIEDER: It depends on the age of the patient. It’s not so much age in and of itself, but [more so] transplant eligible vs ineligible. For a younger, healthier person, typically I would use a 4-drug regimen, but let’s say a 3-drug regimen, mostly bortezomib [Velcade], lenalidomide [Revlimid], and dexamethasone [VRd], as opposed to adding daratumumab [Darzalex], just because of comfort and having prescribed [that...
triplet] over the years. But the daratumumab regimen, D-VRd, is certainly very reasonable and probably just as good as the VRd regimen.

**BRAUNSTEIN:** I think they’re both highly effective regimens, with perhaps deeper responses [achieved] by adding daratumumab, but still both highly effective. Does anybody else want to share their practice pattern, what they prefer as a triplet or quadruplet regimen up front?

**ALI:** I agree with VRd or D-VRd. Both are good, I think, for transplant-eligible patients, as you mentioned, and both are very well tolerated.

**BRAUNSTEIN:** It seems like we’re a fairly homogenous group in terms of favoring VRd. For patients who present with renal failure and who maybe have a creatinine clearance less than 40 mL/min—in this case, it was 45 mL/min—I might consider starting with cyclophosphamide [Cytoxan], bortezomib, and dexamethasone [CyBorD] or daratumumab plus CyBorD and then switching to lenalidomide after 1 cycle if their creatinine clearance improves.

Dr Wieder, you spoke about the fitness or transplant eligibility of the patient. Are there any particular comorbidities that would lead you more toward a quadruple regimen with a monoclonal antibody [vs] a triplet regimen, or does every patient just get a quad up front because it’s the most intensive regimen we have?

**WIEDER:** Typically, I haven’t been using much of the quadruplet regimens, because I haven’t had a lot of experience with it, I think that the toxicity is definitely higher, and I’m not sure how much more [advantage] you’re going to get from it. You definitely get a better response. The question is, is it so much better that it’s worth it, to get the patients to transplant? So I’ve been doing mostly triplets, but I think in a very young patient who has bulky disease, if they could tolerate it, the main option that I would consider would be a 4-drug vs a 3-drug regimen.

**BRAUNSTEIN:** If you had a patient you felt would benefit from a 4-drug regimen, are there any particular comorbidities that would make you a little more hesitant to give a 4-drug regimen?

**WIEDER:** Not in particular. I think that lenalidomide should probably be used with caution in kidney disease, but the fourth drug that I’d typically be adding would be daratumumab. I think daratumumab, in and of itself, doesn’t have any specific contraindications to using it, so to me, patients who have a good performance status and few comorbidities can tolerate a 4-drug regimen.

**BRAUNSTEIN:** How about the fact that this patient was anemic to start, which we assume is related to her disease burden? Do you have any hesitation there to use the 4-drug regimen that’s likely to be more myelosuppressive?

**ALI:** No, I would [be more inclined to] use a 4-drug regimen because she’s a young patient, and you are absolutely right, her anemia is secondary to her disease, so we need to control her disease, so we can send her for a possible autologous stem cell transplant [ASCT].

**BRAUNSTEIN:** I completely agree. I think we’re likely to see that anemia improve fairly quickly as you treat her. Another way of phrasing the question: If you have a patient who’s not transplant eligible, do you use a 4-drug regimen or do you give triplets or doublets?

**WIEDER:** I think [I would avoid using a] 4-drug regimen on those patients for 2 reasons. First of all, the things that are making them transplant ineligible [ie, age or comorbidities] are the same things that would make it very difficult for them to tolerate a 4-drug regimen. [Second,] with a transplant-ineligible patient I don’t want to use up all my weapons at the same time, and I’m not sure how much more [benefit] you’re getting with the 4-drug regimen. I’d rather use the drugs sequentially, rather than together, because I think there might be some added benefit. There’s definitely [greater] toxicity with a 4-drug regimen. [When] sequencing the drugs, one after the other or alternating triplets, I’m not sure the patient is losing out on much.

**BRAUNSTEIN:** Exactly, and I agree. What makes a patient transplant ineligible may also make them less fit—if we’re talking about fitness.

**DISCUSSION QUESTIONS**

- How do you manage adverse events (AEs) for patients receiving induction therapy?
  - Does it differ for triplet vs quadruplet therapy?

**BRAUNSTEIN:** Our new oncology fellows just started this past week, and they’re learning the art of how to manage AEs, and we tell them about the different things you can do. You can pause [treatment], you can try to suppress [the AEs], or you can dose reduce. In your experience, which of those options have you had to do, primarily, for patients getting quadruplets or triplets for induction for multiple myeloma, if at all? Maybe you haven’t had any issues and just plowed through the treatment.

**BLOKH:** I have had a pretty good experience, in that most of my patients breezed through the triplets and even the...
WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis: Hypertension was reported in 45% of FOTIVDA-treated patients with 22% of the events ≥Grade 3. Hypertensive crises were reported in 0.6% of patients. Do not initiate FOTIVDA in patients with uncontrolled hypertension. Monitor for hypertension and treat as needed. Reduce the FOTIVDA dose for persistent hypertension not controlled by anti-hypertensive medications. Discontinue FOTIVDA for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Cardiac Failure: Cardiac failures were reported in 1.6% of FOTIVDA-treated patients, with 1% of events reported as ≥Grade 3. 0.6% of events were fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with FOTIVDA. Manage with dose interruption, dose reduction, or discontinuation.

Cardiac Ischemia and Arterial Thromboembolic Events: Cardiac ischemia in FOTIVDA-treated patients were reported in 3.2%; 0.4% of events were fatal. Arterial thromboembolic events were reported in 2.0% of FOTIVDA-treated patients, including death due to ischemic stroke (0.1%). Closely monitor patients who are at risk for, or who have a history of these events. Discontinue FOTIVDA in patients who develop severe arterial thromboembolic events, such as myocardial infarction and stroke.

Venous Thrombotic Events: Venous thromboembolic events were reported in 2.4% of FOTIVDA-treated patients, including 0.3% fatal events. Closely monitor patients who are at increased risk for these events. Discontinue FOTIVDA in patients who develop serious venous thromboembolic events.

Hemorrhagic Events: Hemorrhagic events were reported in 11% of FOTIVDA-treated patients; 0.2% of events were fatal. FOTIVDA should be used with caution in patients who are at risk for or who have a history of bleeding.

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INDICATIONS

FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

IMPORTANT SAFETY INFORMATION

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Proteinuria: Proteinuria was reported in 8% of FOTIVDA-treated patients, with 2% Grade 3. Monitor throughout treatment with FOTIVDA. For moderate to severe proteinuria, reduce the dose or interrupt treatment with FOTIVDA. Discontinue FOTIVDA in patients who develop nephrotic syndrome.

Thyroid Dysfunction: Thyroid dysfunction events were reported in 11% of FOTIVDA-treated patients, with 0.5% of events reported as ≥Grade 3. Monitor thyroid function before initiation and throughout treatment with FOTIVDA.

Wound Healing Complications: Withhold FOTIVDA for at least 24 days prior to elective surgery. Do not administer FOTIVDA for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of FOTIVDA after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by MRI, can occur with FOTIVDA. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FOTIVDA if signs or symptoms of RPLS occur.

Embryo-fetal Toxicity: FOTIVDA can cause fetal harm. Advise patients of the potential risk to a fetus, to avoid becoming pregnant and to use contraception during treatment and for one month after the last dose of FOTIVDA. Advise males with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose of FOTIVDA.

Allergic Reaction to Tartrazine: FOTIVDA 0.89 mg capsule contains FD&C Yellow No. 5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients.

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WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis: Hypertension was reported in 45% of FOTIVDA-treated patients with 22% of the events ≥Grade 3. Hypertensive crises were reported in 0.6% of patients. Do not initiate FOTIVDA in patients with uncontrolled hypertension. Monitor for hypertension and treat as needed. Reduce the FOTIVDA dose for persistent hypertension not controlled by anti-hypertensive medications. Discontinue FOTIVDA for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Cardiac Failure: Cardiac failures were reported in 1.6% of FOTIVDA-treated patients, with 1% of events reported as ≥Grade 3. 0.6% of events were fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with FOTIVDA. Manage with dose interruption, dose reduction, or discontinuation.

Cardiac Ischemia and Arterial Thromboembolic Events: Cardiac ischemia in FOTIVDA-treated patients were reported in 3.2%; 0.4% of events were fatal. Arterial thromboembolic events were reported in 2.0% of FOTIVDA-treated patients, including death due to ischemic stroke (0.1%). Closely monitor patients who are at risk for, or who have a history of these events. Discontinue FOTIVDA in patients who develop severe arterial thromboembolic events, such as myocardial infarction and stroke.

Venous Thrombotic Events: Venous thromboembolic events were reported in 2.4% of FOTIVDA-treated patients, including 0.3% fatal events. Closely monitor patients who are at increased risk for these events. Discontinue FOTIVDA in patients who develop serious venous thromboembolic events.

Hemorrhagic Events: Hemorrhagic events were reported in 11% of FOTIVDA-treated patients; 0.2% of events were fatal. FOTIVDA should be used with caution in patients who are at risk for or who have a history of bleeding.

Proteinuria: Proteinuria was reported in 8% of FOTIVDA-treated patients, with 2% Grade 3. Monitor throughout treatment with FOTIVDA. For moderate to severe proteinuria, reduce the dose or interrupt treatment with FOTIVDA. Discontinue FOTIVDA in patients who develop nephrotic syndrome.

Thyroid Dysfunction: Thyroid dysfunction events were reported in 11% of FOTIVDA-treated patients, with 0.5% of events reported as ≥Grade 3. Monitor thyroid function before initiation and throughout treatment with FOTIVDA.

Wound Healing Complications: Withhold FOTIVDA for at least 24 days prior to elective surgery. Do not administer FOTIVDA for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of FOTIVDA after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by MRI, can occur with FOTIVDA. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FOTIVDA if signs or symptoms of RPLS occur.

Embryo-fetal Toxicity: FOTIVDA can cause fetal harm. Advise patients of the potential risk to a fetus, to avoid becoming pregnant and to use contraception during treatment and for one month after the last dose of FOTIVDA. Advise males with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose of FOTIVDA.

Allergic Reaction to Tartrazine: FOTIVDA 0.89 mg capsule contains FD&C Yellow No. 5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients.
Venous Thrombotic Events:

Venous thromboembolic events were reported in 0.2% of events were fatal. FOTIVDA should be used with patients who develop serious venous thromboembolic events.

Arterial thromboembolic events were reported in 2.0% of FOTIVDA-treated patients. FOTIVDA in patients who develop severe arterial thromboembolic events, such as myocardial infarction and stroke. Discontinue FOTIVDA for patients who are at risk for, or who have a history of these events. Discontinue FOTIVDA-treated patients were reported in 3.2%; 0.4% of events were fatal.

Hypertension and Hypertensive Crisis:

Hypertension was reported in 45% of FOTIVDA-treated patients with 22% of the events ≥Grade 3. Hypertensive crises were reported in 0.8% of patients. Do not initiate FOTIVDA in patients of FOTIVDA-treated patients with hypertension that cannot be controlled with anti-hypertensive medications. Discontinue FOTIVDA for severe hypertension not controlled by anti-hypertensive medications. Reduce the FOTIVDA dose for persistent hypertension not needed. Evaluate for RPLS in patients presenting with seizures, headache, hypertension, and impaired consciousness.

Hypertensive crises were reported in 0.8% of patients. Do not initiate FOTIVDA in patients with 2% Grade 3. Monitor throughout treatment with FOTIVDA. For moderate hypertension, reduce the dose or interrupt treatment with FOTIVDA.

Thyroid Dysfunction:

Thyroid dysfunction events were reported in 11% of FOTIVDA-treated patients, with 2% Grade 3. Monitor throughout treatment with FOTIVDA. For moderate hyperthyroidism, reduce the dose or interrupt treatment with FOTIVDA.

Proteinuria was reported in 8% of FOTIVDA-treated patients, with 2% Grade 3. Monitor throughout treatment with FOTIVDA. For moderate proteinuria, reduce the dose or interrupt treatment with FOTIVDA.

To report SUSPECTED ADVERSE REACTIONS, contact AVEO Pharmaceuticals, Inc. at 1-833-FOTIVDA (1-833-368-4832) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the brief summary of the Prescribing Information for FOTIVDA® (tivozanib) on the following pages.

5.7 Thyroid Dysfunction
FOTIVDA can cause thyroid dysfunction. Thyroid dysfunction events in FOTIVDA-treated patients occurred in 1% of patients treated with FOTIVDA, 12% of patients treated with FOTIVDA vs. 3% of patients treated with sorafenib. Thyrotoxicosis was reported in 0.8% of patients treated with FOTIVDA, and hypothyroidism was reported in 1% of patients treated with FOTIVDA. Discontinue FOTIVDA if thyroid dysfunction events occur.

5.8 Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway, such as FOTIVDA. Therefore, FOTIVDA has the potential to adversely affect wound healing. Withhold FOTIVDA for at least 24 days 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 FOTIVDA after resolution of wound healing complications has not been established.

5.9 Reversible Posterior Leukoencephalopathy Syndrome
(RPLS), a syndrome of subcortical vasogenic edema diagnosed by MRI, can occur with FOTIVDA. Perform a diagnostic evaluation for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FOTIVDA in patients who develop RPLS.

5.10 Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, FOTIVDA can cause fetal harm when administered to a pregnant woman. In embryo-fetal developmental studies, oral administration of tivozanib to pregnant animals during the period of organogenesis caused maternal toxicity, including fetal malformations and embryo-fetal death at doses below the maximum recommended clinical dose on a mg/m² basis.

5.11 Allergic Reactions to Tartrazine
FOTIVDA contains tartrazine. Patients with a history of hypersensitivity reactions to tartrazine and other xanthine esters may have an increased risk of experiencing an allergic reaction to FOTIVDA.

5.12 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.13 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.14 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.15 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.16 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.17 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.18 Proteinuria
Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 38% (3.7%) had acute kidney injury concurrently or later during treatment. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.
Clinically relevant adverse reactions in <15% of patients who received FOTIVDA included venous, venous thromboembolism, arterial thromboembolism, hyperthyroidism, hepatobiliary disorders, osteonecrosis, cardiac failure, and delirium.

Table 3 summarizes the laboratory abnormalities in TIVO-3.

<table>
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<th>Laboratory Abnormality</th>
<th>FOTIVDA (n = 173)</th>
<th>Sorafenib (n = 170)</th>
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<tr>
<td>All Grades (%)</td>
<td>Grades 3 Or 4 (%)</td>
<td>All Grades (%)</td>
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<tr>
<td>Hematology</td>
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<tr>
<td>Lymphocytes decreased</td>
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In an embryo-fetal developmental study in pregnant rabbits, daily oral administration of tivozanib at 1 mg/kg/day (1.5 times the maximum recommended clinical dose on a mg/m² basis) during the period of organogenesis resulted in fetal malformations including ventricular septal defects and major vessel anomalies. No maternal toxicity was reported at doses up to 1 mg/kg/day.

8.2 Lactation: Risk Summary. There are no data on the presence of tivozanib in human milk, or the effects of tivozanib on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with FOTIVDA and for one month after the last dose.

8.3 Females and Males of Reproductive Potential FOTIVDA can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing: Verify pregnancy status of females of reproductive potential prior to starting treatment with FOTIVDA.

Contraception: Advise females of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose.

Infertility: Based on findings in animal studies, FOTIVDA can impair fertility in females and males of reproductive potential.

8.4 Pediatric Use. The safety and effectiveness of FOTIVDA in pediatric patients have not been established.

8.5 Geriatric Use. Of the 1008 patients with advanced RCC treated with FOTIVDA, 29% were ≥65 years of age and 4% were ≥75 years of age. No overall differences in effectiveness were observed between patients ≥65 years versus <65 years of age. Of the 175 patients with advanced RCC following two or more prior systemic therapies randomized to FOTIVDA, 29% were ≥65 years of age and 6% were ≥75 years of age. No overall differences in effectiveness were observed between patients ≥65 years versus <65 years of age.

8.6 Renal Impairment. No dosage modification is recommended for patients with mild to severe renal impairment (creatinine clearance [CLcr] 15-89 mL/min, estimated by Cockcroft-Gault). The recommended dosage for patients with end-stage renal disease has not been established.

8.7 Hepatic Impairment. Reduce the dosage when administering FOTIVDA in patients with moderate total bilirubin (3.0-3.9 mg/dL) or AST greater than 1.5 times ULN with any AST hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1.5 times ULN with any AST) hepatic impairment. The recommended dosage of FOTIVDA in patients with severe (total bilirubin greater than 3 to 10 times ULN with any AST) hepatic impairment has not been established.

10 OVERDOSAGE. Overdose with FOTIVDA can cause severe hypertension and hypertensive crisis that may result in death.

During clinical studies, three patients inadvertently received doses ≥2.68 mg (≥2 times the recommended dose) of FOTIVDA. One patient who received two daily doses of 8.9 mg of FOTIVDA experienced hypertensive crisis with severe hypertensive retinopathy; a second patient who received three doses of 1.34 mg in one day experienced fatal uncontrolled hypertension; and a third patient who received two doses of 1.34 mg FOTIVDA in one day experienced persistent hypertension lasting over 3 days. There is no specific treatment or antidote for FOTIVDA overdose. In cases of suspected overdose, withhold FOTIVDA, closely monitor patients for hypertension and hypertensive crisis and other potential adverse reactions. Immediately manage signs or symptoms of hypertension and provide other supportive care as clinically indicated.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (PATIENT INFORMATION).

Hypertension and Hypertensive Crisis: Informs patients that hypertension or hypertensive crisis may occur during FOTIVDA treatment. Advise patients to undergo routine blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated.

Cardiac Failure: Advise patients that if they experience signs or symptoms of hypertension to immediately contact their health care provider.

Cardiac Ischemia and Arterial Thromboembolic Events. Advise patients that arterial thromboembolic events (including fatal outcomes) may occur during FOTIVDA treatment. Advise patients to immediately contact their health care provider if new onset of chest discomfort, sudden weakness, or other events suggestive of a thrombotic event occurs.

Venous Thromboembolic Events. Advise patients to immediately contact their healthcare provider if they develop symptoms of dyspnea or localized limb edema.

Drug Interactions: Advise patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual bleeding or hemorrhage.

Risk of Impaired Wound Healing: Informs patients that FOTIVDA may impair wound healing. Advise patients that temporary interruption of FOTIVDA is recommended prior to elective surgery. Advise patients to contact their healthcare provider before any planned surgeries, including dental surgery.

Reversible Posterior Leukoencephalopathy Syndrome: Informs patients that RPLS may occur during FOTIVDA treatment. Advise patients to immediately contact their healthcare provider in the event of seizures, headaches, visual disturbances, confusion, or difficulty thinking.

Overdosage: Instruct patients to contact their healthcare provider immediately if they inadvertently take too much FOTIVDA.

Embyro-Fetal Toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose.

Lactation: Advise women not to breastfeed during treatment with FOTIVDA and for one month after the last dose.

Infertility: Advise males and females of reproductive potential that FOTIVDA can impair fertility.

Important Administration Information: Instruct patients if a dose of FOTIVDA is missed, the next dose should be taken at the regular scheduled time. Do not take two doses in the same day.

Drug Interactions: Advise patients to inform their healthcare provider of all concomitant medications, vitamins, or dietary and herbal supplements.

This brief summary is based on the FOTIVDA Prescribing Information issued 02/2021.

[One exception is] a patient that I’m still [treating], who has had persistent leukopenia and even neutropenia. Initially, I gave her a daratumumab-based triplet. [Then] I got rid of the daratumumab and the lenalidomide, and then I tried to observe her, and as soon as I gave lenalidomide again, her white blood cell count dropped again. Now I have her on bare-bones bortezomib and dexamethasone, and she still runs low with her white blood cell count. I’m not going to assess the bone marrow, because she has been dropping her [blood cell] counts from the beginning of her treatment, so I think it’s treatment related. I don’t know what to do with her; I’m just giving her filgrastim [Neupogen] shots.

It’s not myelotoxic chemotherapy, so you can give filgrastim shots throughout the process, unlike the precautions we take with traditional chemotherapy. So I give her bortezomib and dexamethasone, and I give her 3 days’ worth of filgrastim shots after the regimen, but she’s coming to the infusion center almost every day of the week, and I don’t know what to do with her in terms of the neutropenia.

BRAUNSTEIN: Yes, there are patients who tend to be more sensitive to these drugs, and you can’t always predict it, and you run into those problems. I totally agree with you; I would give the patient growth factors to try to get them through therapy and not deprive them of the benefit of one of the drugs in the class. There are certainly patients who will develop thrombocytopenia or neutropenia. You can’t dose reduce the daratumumab, but you can try to dose reduce the lenalidomide or the bortezomib. I don’t think it’s unreasonable to give growth factors just to try to get them through, especially in the beginning when they may have less bone marrow reserve because their disease burden is higher. I agree—in my practice I haven’t had that many patients who needed to be admitted for grade 3 or 4 neutropenia fever, but we always worry about infections in these patients at diagnosis.

WIEDER: The drugs are, in my experience, very well tolerated. Any time you use any drug for a long period of time, it’s potentially going to cause some chronic neuropathy and so on. But usually, when you use an induction regimen [for] 4 to 6 cycles, it’s very uncommon that you get any major AEs. The 1 issue that I’ve run into lately, more often than not, is a lenalidomide-[related] rash. I think that’s relatively common compared with some of the other potential AEs. For that issue, I usually hold [the drug], wait for the rash to resolve, and then I reintroduce the drug at a lower dose. But aside from that, I find that the drugs are tolerated very well.

BRAUNSTEIN: Right, I agree. The lenalidomide rash creeps up on you. It’s hard to predict, and it’s something that patients will always call me about because they notice it early on. I try to give topical hydrocortisone or antihistamines or something to try to suppress it just to get them through. And most of the time that does the trick, but sometimes we have to dose reduce....That can be a challenge sometimes.
BRAUNSTEIN: Yes, I think that’s perfectly fair. I think if a patient is minimal residual disease [MRD] negative after transplant, you can probably forgo those 2 cycles of consolidation and go right to maintenance. That’s just my practice pattern, but there is an ongoing randomized study [AURIGA; NCT03901963] of patients who are MRD positive after transplant [randomly assigned] to daratumumab plus lenalidomide vs lenalidomide alone. It hasn’t been read out yet.

CHEUNG: Is MRD measured on peripheral blood or on bone marrow? [And is] MRD a useful way to determine [whether] patients [should] go on maintenance or continue maintenance?

BRAUNSTEIN: There’s no peripheral blood assay yet to do MRD testing for multiple myeloma. It is all done with bone marrow samples. The clonoSEQ assay, which is the only FDA-approved assay for looking at MRD status, uses next-generation sequencing of the patient-specific multiple myeloma rearrangement to determine MRD.

The second question is, essentially, how do you practically use MRD? And does it determine your choice about whether a patient should go on maintenance? The MASTER study [NCT03224507] tried to address this question of [using] MRD negativity to de-escalate therapy. I think that’s an evolution in how we make decisions based on MRD.

[Maintenance therapy] remains the standard of care after transplant, regardless of MRD status, but there are newer studies that are looking to see if it’s OK to say, “[If you are] MRD negative, you don’t need to get more maintenance therapy,” which has its own potential AEs. But for now, the convention is still to give maintenance therapy after transplant because it has been shown to improve survival, [although] those survival studies were done before the prevalence of MRD as a clinical tool for multiple myeloma assessment. I would still probably give maintenance therapy, even if the patient were MRD negative.

To anybody else: if you’ve given the quadruplet up front, do you give dual-agent maintenance or single agent?

ALI: [The] transplant specialist usually recommends what to do, how much lenalidomide [to give]. We usually follow that. If a patient becomes MRD negative from induction treatment, will you send them for transplant at that time?

BRAUNSTEIN: To some extent, it depends upon who you’re asking. The transplanters will tell you that MRD is not perfect and that you could still have residual disease. And we know that the patient is likely to relapse at some point eventually, anyway, that they may not be fit enough down the road for a salvage transplant, and that despite the MRD data we have now, [transplant] has still been shown to have progression-free survival [PFS] benefit and, in some studies, overall survival [OS] benefit.

Those who don’t favor transplant up front will point to [results from] the [IFM/DFCI2009] study [NCT01191060] and the DETERMINATION study [NCT01208662], which showed that patients in the nontransplant arm[s] still achieved MRD negativity, and they seemed to do just as well as the transplant group[s].\(^1,2,5\) I think it’s probably practice dependent. Personally, I would probably still pursue the transplant, just because the PFS rates were higher, and in the GRIFFIN study, [treatment] was combined with transplant, and they didn’t use MRD to determine whether patients were going to go for transplant.\(^1,6\) But I think we need more data to pin down the answer to that question and determine whether you can use MRD prior to transplant to [determine] if the transplant is critical up front. I think it’s institution dependent.

BLOKH: We used to give bortezomib for patients with high-risk cytogenetics and lenalidomide for everyone else, 10 mg once a day, until disease progression. But now I’m noticing that daratumumab is creeping up in the maintenance setting. In what situations would you use daratumumab vs bortezomib?
BRAUNSTEIN: The National Comprehensive Cancer Network guidelines still recommend maintenance with either bortezomib or lenalidomide plus bortezomib for higher-risk patients. To date, I’m not aware of any data showing that daratumumab maintenance impacts the high-risk patients more than single-agent bortezomib or lenalidomide. But there are data [showing] that including proteasome inhibitors, and maybe even dual-agent bortezomib plus lenalidomide, leads to better outcomes for patients with high-risk features. The consensus is to treat high-risk patients as intensely as possible, and that probably translates into the maintenance setting as well, but we don’t have the data to answer that yet.

In the FORTE study [NCT02203643], where patients got carfilzomib [Kyprolis] plus lenalidomide maintenance, the high-risk group didn’t necessarily do better in the subgroup analysis, so I’m not sure we know exactly how to best treat the high-risk patients in the maintenance setting, in terms of using daratumumab or not.

DISCUSSION QUESTIONS

- With the introduction of novel induction therapies, is there a continued role for transplantation in patients with newly diagnosed multiple myeloma?
- Do the results of the DETERMINATION study influence how you consider ASCT?

BRAUNSTEIN: I’m interested to know how [the novel induction therapies] influence your choice of transplant. I know you may defer that decision to the transplanter, but do the results of the IFM 2009 study and the DETERMINATION study [NCT01208662], which were fairly similar in their outcomes in showing PFS [benefit] but not necessarily OS [benefit], impact your decision on whether to give transplants? Do [these results] allow you to stratify patients in terms of who you think might be better suited for transplant?

SIEBEL: For this [decision], I would defer to a transplanter.

BRAUNSTEIN: I think transplanters will likely see [the DETERMINATION study] as being favorable because of the PFS benefit, but I think that it gives you some leverage to discuss with the patient that there are data saying that you could potentially rescue patients with a salvage transplant in subsequent lines of therapy. And, of course, there will be more data with CAR [chimeric antigen receptor] T-cell therapy in earlier lines of therapy, too, and that might impact how we think about transplant. That’s going to take some time.

REFERENCES

**Shah Explores Treatment Options for Patients With Advanced HER2+ Gastric Cancer**

**CASE**

- A 65-year-old man presented with new onset fatigue, upper abdominal pain that worsened with eating, and unintentional weight loss.
- Medical history: lumbar spine osteoarthritis, medically controlled hypertension, prediabetes
- Physical examination: unremarkable
- ECOG performance status: 1

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</table>

**Manish A. Shah, MD**

Director, Gastrointestinal Oncology Program
Professor of Medicine
Weill Cornell Medicine
Chief, Solid Tumor Service
Codirector, Center for Advanced Digestive Disease
NewYork-Presbyterian
New York, NY

**Targeted Oncology**

- **What do you think are the most important data regarding the combination of pembrolizumab and trastuzumab for treating patients with HER2-positive unresectable or metastatic gastric or gastroesophageal cancer?**

**SHAH:** KEYNOTE-811 [NCT03615326] is based on a [prior] phase 2 study [NCT02954536] run by Yelena Y. Janjigian, MD. In that study there was a 91% overall response rate [ORR], so that led to a global phase 3 study of chemotherapy. The investigators used FP or capecitabine plus oxaliplatin [CAPOX]. That way it was an every-3-weeks schedule with trastuzumab and they [randomly assigned] patients to placebo or pembrolizumab. The primary outcome was OS [overall survival]. The second primary end point was PFS [progression-free survival], and ORR was a [key] secondary end point.

In the first interim analysis they were looking at ORR in the first 260 patients, and the total study size was 692, so not even half of all the patients were enrolled. They were looking at the first 260 [patients], and they had a superiority bound with a 1-sided P value of .002. As typical for gastric and GEJ cancers, most [of the patients] were male, and [in terms of geographic location], 31% were in Australia plus a Western population, 30% in Asia, and then the rest of the world was about 40%. Most patients had true stomach cancers [72% in the experimental arm and 68% in the placebo arm]; most had an intestinal [histological subtype]. Most patients with HER2-positive disease are going to be PD-1 positive as well, and [so] 85% to 89% [were PD-1 positive]. Most patients’ HER2 status was IHC 3+. IHC 3+ gastric tumors are driven by HER2, so even without pembrolizumab, I have several patients

*continued on page 43*
See the latest data for SARCLISA + Kd

Explore the full results of the IKEMA phase 3 trial at sarclisahcp.com

Kd=Kyprolis (carfilzomib) and dexamethasone
Who are doing well 3 to 4 years down the line with targeting the HER2 aspect here. Most patients got CAPOX, very few got FP.

The patients who were [randomly assigned] to receive chemotherapy plus trastuzumab plus pembrolizumab had a very high response rate. The ORR was around 74.4%, but about 97% had some decrease in their tumor volume. Radiographically, 11% had a clinical complete response [CR], which is quite tremendous. The duration of response [DOR] was significant; it was a median of about 10 months.

So if you’re responding to this regimen, you’re going to respond well. But in the placebo arm, the DOR was 9.5 months, so it’s also very active. The disease control rate was 96% [with pembrolizumab] vs [89% in the placebo group]. Trastuzumab has a lot of activity, but I think adding pembrolizumab probably does have more activity, and based on that, the FDA did approve pembrolizumab in the first-line setting.

Toxicities were similar in terms of the serious adverse events [AEs], about 30% in both arms. The most common toxicities of grade 3 to 5 were anemia and diarrhea. Those are the most common but [they were] actually less than 10% for both arms. Generally, it was a pretty well-tolerated regimen. In terms of the immune-specific toxicities, infusion reactions [of grade 3 or higher] rarely [occurred], pneumonitis [of grade 3 to 5 occurred at a rate of 1% in the treatment arm and not at all in the placebo arm], [and] colitis of [grade 3 to 5 occurred at a rate of 3% in the treatment arm and 1% in the placebo arm]. I have to be honest, in my practice, I see more grade 3 and 4 [immune-mediated] toxicity than is reported here, which is less than 5%. But in this randomized study, pembrolizumab doesn’t seem to add that much toxicity.

### CASE UPDATE

- Six months later, restaging showed progressive disease with new pulmonary lesions.
- Repeat HER2 IHC was 2+, and FISH (fluorescence in situ hybridization) was positive.

### POLLING QUESTION

During a live, virtual event, Shah asked, “What are you most likely to recommend for this patient?”

- Trastuzumab deruxtecan 62% (5)
- Ramucirumab plus paclitaxel 38% (3)
- Docetaxel or paclitaxel 0% (0)
- Other single-agent or combination chemotherapy 0% (0)

Total votes: 8

What is the role of fam-trastuzumab deruxtecan (Enheru) in treating patients with HER2-positive gastric cancer?

This is an antibody-drug conjugate, and there are 3 components. There’s the humanized anti-HER2 monoclonal antibody, which is very similar to trastuzumab, but the payload is the drug that’s linked to the trastuzumab antibody through a linker, and the payload in this case is a topoisomerase I inhibitor. It’s an exatecan derivative, and then the linker is a tetrapeptide-based cleavable linker. What happens is that the drug binds trastuzumab, gets internalized, and then the topoisomerase I inhibitor gets freed and then can go into the nucleus and bind [and inhibit] topoisomerase I. The other thing is the drug-to-antibody ratio, or DAR. For the other HER2-targeted antibody-drug conjugate, it’s T-DM1, which is trastuzumab with emtansine [Kadcyla], and for that one, the DAR is 4.

This drug-antibody conjugate has a DAR of 8, [which] is pretty high. So you’re getting a lot of drug in with the antibody.

The DESTINY-Gastric01 study [NCT03329690] is a study [that randomly assigned patients to receive] trastuzumab deruxtecan at 6.4 mg/kg vs physician’s choice, [being] chemotherapy—irinotecan [Camptosar] or paclitaxel. It was a 2:1 randomization. It was a small study of 188 patients. The arms were well balanced in terms of age and [sex]. It was a study done in Asia only, so most of the patients were from Japan but there were some from South Korea as well. Most patients had IHC 3+ [HER2 expression] but not all. Some tumors were quite big and bulky, but about half the patients’ tumors were less than 5 cm. One hundred percent of patients had prior trastuzumab therapy, so this was truly a trastuzumab-refractory population.

In this trastuzumab-refractory population…trastuzumab deruxtecan had a 51% ORR. It actually went down to 43% after central review, but it’s still a high response. Chemotherapy had a 14% response, and that’s about right for chemotherapy. If you use paclitaxel and ramucirumab [Cyramza], your ORR is [28%]. Some patients had a CR, about 10%, which is quite amazing in this setting.

The PFS [Kaplan-Meier] curves for trastuzumab deruxtecan show [approximately] a 2-month improvement in median PFS [5.6 months vs 3.5 months with chemotherapy], but the tail on the curve is impressive. So 30% of patients are without progression at a year with trastuzumab deruxtecan vs none who got chemotherapy. Initially, maybe half the patients have only marginal benefit, but the tail of the curve is quite impressive. About 25% have quite durable responses going out to 1.5 to 2 years. In terms of median OS, it is much better, [approximately] 12 months if you use trastuzumab deruxtecan vs 8 months with chemotherapy [Figure]. The [Kaplan-Meier] curves split pretty early, and they stay split.

If you look more carefully at who was responding, for the most part it was independent of the number of [prior]
It’s interesting, though, in the HER2 IHC 3+ group, the benefit was quite significant. In the HER2 IHC 2+ [group with only] 44 patients, chemotherapy did about as well as trastuzumab deruxtecan. The benefit was primarily in HER2 IHC 3+, not HER2 IHC 2+ FISH positive. The benefit was equal in gastric or GEJ tumors and perhaps slightly better in diffuse gastric cancer. If you had a total gastrectomy and you got the trastuzumab deruxtecan, you did much better. The numbers are small [n = 31 patients], so I don’t know if that is a fluke, but the confidence limits don’t overlap, so it may be the most significant thing.

In terms of toxicity with chemotherapy vs trastuzumab deruxtecan, chemotherapy is generally pretty well tolerated: [23% grade 3 or 4] anemia, [24% grade 3 or 4] neutropenia. With trastuzumab deruxtecan, the toxicity is a little bit higher, [51% had grade 3 or 4] anemia [and 38% had grade 3 or 4] neutropenia. It does have a little more toxicity than you would see with chemotherapy.

Pneumonitis is probably the most worrisome AE. At the initial experience, there were a handful of [patients] who had grade 5 [pneumonitis], but I think the point is that if you identify it early, at the initial onset of shortness of breath or if you have some findings on a CT scan, you can manage the pneumonitis much better with steroids, holding the drug, and so forth.7

REFERENCES
**Konduri Considers Second-line Options for ES-SCLC**

**CASE**

- A moderately active man, aged 58 years, presented with worsening shortness of breath, persistent dry cough, and fatigue. He is a smoker with a 30 pack-year history. ECOG performance status: 1
- Chest x-ray showed opacity in left lung
- Chest CT showed hilar mass, with invasion of left pulmonary artery and 3 contralateral lung nodules present
- Brain MRI: negative
- Bronchoscopy with transbronchial biopsy/pathology: small cell lung cancer (SCLC)
  - Diagnosis: Extensive-stage SCLC (ES-SCLC)
- He received 4 cycles of carboplatin plus etoposide plus atezolizumab (Tecentriq).
- Initially achieved partial response
- Seven months after his last cycle of platinum chemotherapy, his shortness of breath returned with right upper quadrant pain and mid back pain.
- CT of the chest, abdomen, and pelvis showed recurrence of the left upper lobe mass with hematogenous metastases in the liver and adrenal glands.
- MRI: Negative for brain metastases
- Laboratory results: within normal limits
- ECOG performance status: 1

**Targeted Oncology™: What treatment options are available for this patient with metastatic SCLC and disease progression after platinum-based chemotherapy?**

**KONDURI:** Lurbinectedin’s [Zepzelca] consideration came up from a basket trial [NCT02454972]. It was studied and published by José Trigo, MD, et al.¹ It’s an alkylating agent, which was pulled out from marine life. Patients with SCLC were part of the trial. They had a functional performance status of 0 to 2 and did not have CNS [central nervous system] metastases, so they obviously had to have good function. The dose is 3.2 mg/m² every 3 weeks. There were 105 patients and basically if 15% or less got a response, then the null hypothesis was not proved.

The average number of tumor sites was 3. The patients were mostly smokers and [former] smokers. The stage at diagnosis was mostly ES-SCLC. Some patients had limited-stage SCLC, but that was only one-third of the patients. Paraneoplastic syndromes were present in about 9% of patients. A significant number of patients had bulky disease, about one-third. Patients had 1 or 2 prior lines of therapy, and those included platinum, etoposide, immunotherapy, and even PARP inhibitors, which were being evaluated at that time.

The best response to prior platinum was evaluated. They evaluated the outcomes in patients who [had a median chemotherapy-free interval (CTFI) of less] than 90 days or more than 90 days, which is the cutoff that recently [is used] for resistant...
disease vs patients who have somewhat sensitive disease. For this group, 43% of patients had a CTFI of less than 90 days and 57% had a CTFI greater than 90 days.

The overall response rate [ORR] was 35%. The median progression-free survival [PFS] was 3.5 months, but for patients who had a CTFI of less than 90 days, it was 2.6 months, and for those with more than 90 days, it was 4.6 months [Table 1]. The median overall survival [OS] was 9.3 months, but 5.0 months for patients with a CTFI of less than 90 days and 11.9 months for those with a CTFI of more than 90 days. It was a single-arm trial.

[There were 20 patients in that whole subset who had a CTFI of more than 180 days, and their median OS was 16.2 months compared with the 11.9 months for those with a CTFI of 90 days or more.]

What is the history of the use of topotecan for patients with SCLC platinum-sensitive disease, and what is its role in patients who progressed at least 60 days after first-line chemotherapy?

I talked about a 9-month [median] OS for patients on lurbinectedin. Topotecan [Hycamint] started in 1999 as a drug [that] was compared with CAV [cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin)]. At that time their cutoff for progression was 60 days. They found that when you compare CAV vs topotecan, there are no differences in response rate, duration of response [DOR], time to progression, or OS. The reason it has a consideration for use is because there is an improvement in quality of life, as well as the fact that it was a noninferiority analysis. So, it got approved and topotecan became...a standard.

That’s how topotecan started its journey in SCLC. The 090 trial [SKF104864/090] showed some improvements in shortness of breath, fatigue, hoarseness, cough, etc. But it does not have any significant differences in terms of ORR, DOR, or time to progression.3

The ORR was approximately 24% for topotecan vs 18% for CAV, and then the OS was 5.8 months for topotecan vs 5.7 months for CAV. There is some improvement and oncologic efficacy of topotecan, especially if you compare it with best supportive care, but with CAV, which was the ongoing standard at that time, it did not have a significant difference. Of course, topotecan is a 5-day infusion. This trial had a 28% febrile neutropenia risk. One obviously has to consider using either growth factor support, and now there is the new inhibitor of CDK4/6, trilaciclib [Cosela], to reduce neutropenia.

What data support the NCCN (National Comprehensive Cancer Network) SCLC panel recommendation for platinum rechallenge?

Platinum rechallenge is being reevaluated because of a randomized phase 3 trial called GFPC 01–2013 [NCT02738346]. It got published in 2020.4 It [treated patients with] carboplatin plus etoposide vs topotecan. This was in the second-line setting, and these are

### Table. Selected Efficacy Outcomes of Phase 2 Study of Lurbinectedin for SCLC

<table>
<thead>
<tr>
<th></th>
<th>ALL PATIENTS (n = 105)</th>
<th>CTFI &lt; 90 DAYS (n = 45)</th>
<th>CTFI ≥ 90 DAYS (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>5.3 (4.1-6.4)</td>
<td>4.7 (2.6-5.6)</td>
<td>6.2 (3.5-7.3)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.5 (2.6-4.3)</td>
<td>2.6 (1.3-3.9)</td>
<td>4.6 (2.8-6.5)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>9.3 (6.3-11.8)</td>
<td>5.0 (4.1-6.3)</td>
<td>11.9 (9.7-16.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>63% (n = 66)</td>
<td>82% (n = 37)</td>
<td>48% (n = 29)</td>
</tr>
</tbody>
</table>

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

*Median 17.1 months’ follow-up.
patients who are all the way up to more than 90 days after completion of first-line treatment. The average progression points from first-line chemotherapy were between 127 and 129 days. So, 70% of the patients had progression in less than 180 days. There were some patients who progressed after more than 180 days.4

The median PFS is 4.7 months for the platinum arm vs 2.7 months for topotecan [HR, 0.57; 90% CI, 0.41-0.73; \( P = .0041 \)]. The ORR was 49% for the platinum arm vs 25% for topotecan [\( P = .0024 \)]. The median OS was no different at 7.5 months for the platinum arm vs 7.4 months for topotecan [HR, 1.03; 95% CI, 0.87-1.19; \( P = .94 \)]. [These are] the data that guided platinum rechallenge.4

There is some improvement in terms of toxicities when you look at it in comparison to topotecan. My understanding is that this was part of the reason that it got the 3-month-to-6-month relapse consideration for the NCCN guidelines.5 Because it’s a randomized phase 3 trial, it had more standard data.

From the platinum rechallenge data, I would like to point out one trial by Wakuda et al had a CTFI greater than 180 days, but the number of patients was 11 and their median OS was [14.2] months.4 Remember the data from lurbinectedin was an OS of 16.2 months for the 20 patients with a CTFI of greater than 180 days.2 Of course, this is based upon a basket trial, not an individualized set, but I’m just trying to draw some comparisons.

The median OS in patients who have a CTFI of more than 90 days or more than 180 days hovers in the range [of 7.5 months to (14.2) months].4,6 Many of these trials were retrospective.

[North Japan Lung Cancer Study Group trial 0702, a phase 2 randomized trial by] Inoue et al, compared amrubicin [Calsed] with topotecan. The median OS was 14.3 months, but this is a small phase 2 trial with 30 patients.7 The problem is there is no standardization in the literature. The amrubicin arm actually had good response curves. [Amrubicin] didn’t make the cut because it did not have an improvement in survival compared with topotecan. But its response rates are good.

The data suggest that if they have a CTFI of 180 days or more, they will get a good response. That is my personal interpretation. How do you parse the consideration between one drug vs the other? It’s very hard for me to clarify. Obviously, there is the feeling that if you use chemotherapy, after another 6 months or 8 months you have the possibility to consider a rechallenge.

REFERENCES


Unmet Needs and Future Directions in Extensive-Stage SCLC

Hossein Borghaei, DO, provides advice to researchers about the importance of clinical trials in the setting of extensive-stage small cell lung cancer.

View more at: TargetedOnc.com/link/1999
Provide the first approved CD79b-directed antibody-drug conjugate for R/R DLBCL, NOS, after at least 2 prior therapies

**Indication**

POLIVY in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least 2 prior therapies. Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**Important Safety Information**

**Peripheral Neuropathy**

POLIVY can cause peripheral neuropathy, including severe cases. Peripheral neuropathy occurs as early as the first cycle of treatment and is cumulative. POLIVY may exacerbate preexisting peripheral neuropathy.

In Study GO29365, of 173 patients treated with POLIVY, 40% reported new or worsening peripheral neuropathy, with a median time to onset of 2.1 months. Monitor for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of POLIVY.

**Infusion-Related Reactions**

POLIVY can cause infusion-related reactions, including severe cases. Delayed infusion-related reactions as late as 24 hours after receiving POLIVY have occurred. With premedication, 7% of patients (12/173) in Study GO29365 reported infusion-related reactions after administration of POLIVY.

Administer an antihistamine and an antipyretic prior to the administration of POLIVY, and monitor patients closely throughout the infusion. If an infusion-related reaction occurs, slow or interrupt the infusion and institute appropriate medical management.

**Hepatotoxicity**

POLIVY can cause hepatotoxicity, including elevations of transaminases and/or alkaline phosphatase. Cytopenias were the most common infection-related deaths were reported in 2.9% of patients within 90 days of last treatment. Serious adverse reactions occurred in at least 2 months after the last dose. Monitor complete blood counts throughout treatment.

**Myelosuppression**

Treatment with POLIVY can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In patients treated with POLIVY plus bendamustine and a rituximab product (BR) (n=45), 42% received primary prophylaxis with granulocyte colony-stimulating factor. Cytopenias were the most common reason for treatment discontinuation (18% of all patients). Monitor complete blood counts throughout treatment. Cytopenias may require a delay, dose reduction, or discontinuation of POLIVY. Consider prophylactic granulocyte colony-stimulating factor administration.

**Serious and Opportunistic Infections**

Fatal and/or serious infections, including opportunistic infections such as sepsis, pneumonia (including *Pneumocystis jiroveci* and other fungal pneumonia), herpesvirus infection, and cytomegalovirus infection have occurred in patients treated with POLIVY. Grade 3 or higher infections occurred in 32% (55/173) of patients treated with POLIVY. Infection-related deaths were reported in 2.9% of patients within 90 days of last treatment.

Closely monitor patients during treatment for signs of infection. Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus.

**Progressive Multifocal Leuкоencephalopathy (PML)**

PML has been reported after treatment with POLIVY (0.6%, 1/173). Monitor for new or worsening neurological, cognitive, or behavioral changes. Hold POLIVY and any concomitant chemotherapy if PML is suspected, and permanently discontinue if the diagnosis is confirmed.

**Tumor Lysis Syndrome (TLS)**

POLIVY may cause TLS. Patients with high tumor burden and rapidly proliferating tumors may be at increased risk of TLS. Monitor closely and take appropriate measures, including TLS prophylaxis.
Twice the response and double the duration with POLIVY®+BR* vs BR1

Hepatotoxicity
Serious cases of hepatotoxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with POLIVY. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level.

Embryo-Fetal Toxicity
Based on the mechanism of action and findings from animal studies, POLIVY can cause fetal harm when administered to a pregnant woman. When administered to rats, the small molecule component of POLIVY, monomethyl auristatin E, caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities, at exposures below those occurring clinically at the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraceptive to use effective contraception during treatment with POLIVY and for at least 5 months after the last dose.

Lactation
Advise women not to breastfeed during treatment with POLIVY and for at least 2 months after the last dose.

The Most Common Adverse Reactions
The most common adverse reactions (≥20%) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

In Study G029365, fatal adverse reactions occurred in 7% of recipients of POLIVY plus bendamustine and a rituximab product (BR) (n=45) within 90 days of last treatment. Serious adverse reactions occurred in 64% of patients, most often from infection. Serious adverse reactions occurring in ≥5% of recipients of POLIVY plus BR included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%).

Safety was also evaluated in 173 adult patients with relapsed or refractory lymphoma who received POLIVY, bendamustine, and either a rituximab product or obinutuzumab in Study G029365, including the 45 patients with DLBCL. Fatal adverse reactions occurred in 4.6% of recipients of POLIVY within 90 days of last treatment, with infection as a leading cause. Serious adverse reactions occurred in 60%, most often from infection. Adverse reactions occurring in ≥20% of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting. Infected-related adverse reactions occurring in >10% of patients included upper respiratory tract infection, febrile neutropenia, pneumonia, and herpesvirus infection.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see a brief summary of the Prescribing Information on the following pages.

BOR=best overall response; CDR79b=cluster of differentiation 79b; CR=complete response; DLBCL=diffuse large B-cell lymphoma; DoR=duration of response; EOT=end of treatment; HSCT=hematopoietic stem cell transplantation; IRC=Independent review committee; MMAE=monomethyl auristatin E; NOS=not otherwise specified; PR=partial response; R/R=refractory for refractory.

Following premedication with an antihistamine and antipyretic, POLIVY 1.8 mg/kg was administered by intravenous infusion on Day 2 of Cycle 1 and on Day 1 of Cycles 2–9, with a cycle length of 21 days. Patients received 80 mg/m² daily of POLIVY administered on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of Cycles 2–9. A rituximab product dosed at 375 mg/m² was administered intravenously on Day 1 of each cycle. Granulocyte colony-stimulating factor primary prophylaxis was optional and administered to 42% of recipients of POLIVY plus BR.

In POLIVY-treated patients (n = 45), the median age was 67 years (range 33–86) with 58% being ≥ age 65, 69% were male, 69% white, and 43% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial required an absolute neutrophil count ≥1500/μL, platelet count ≥75,000/μL, creatinine clearance (CrCl) ≥40 mL/min, hepatic transaminases ≤2.5 times upper limit of normal (ULN), and alanine transaminase ≤1.5 times ULN, unless abnormalities were from the underlying disease. Patients with Grade 2 or higher peripheral neuropathy or prior allogeneic hematopoietic stem cell transplantation (HSCT) were excluded.

Patients treated with POLIVY plus BR received a median of 5 cycles, with 49% receiving 6 cycles. Patients treated with BR alone received a median of 3 cycles, with 23% receiving 6 cycles. Fatal adverse reactions occurred in 7% of recipients of POLIVY plus BR within 90 days of last treatment. Serious adverse reactions occurred in 64%, most often from infection. Serious adverse reactions in ≥5% of recipients of POLIVY plus BR included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%).

In recipients of POLIVY plus BR, adverse reactions led to dose reduction in 18%, dose interruption in 51%, and permanent discontinuation of all treatment in 31%. The most common adverse reactions leading to treatment discontinuation were thrombocytopenia and/or neutropenia. Table 4 summarizes commonly reported adverse reactions. In recipients of POLIVY plus BR, adverse reactions in ≥20% of patients included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

### Table 4  Adverse Reactions Occurring in ≥10% of Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

<table>
<thead>
<tr>
<th>Adverse Reactions by Body System</th>
<th>POLIVY + BR</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphoid System Disorders</strong></td>
<td>All Grades, %</td>
<td>Grade 3 or Higher, %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 42</td>
<td>44 36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49 40</td>
<td>33 26</td>
</tr>
<tr>
<td>Anemia</td>
<td>47 24</td>
<td>28 18</td>
</tr>
<tr>
<td><strong>Musculoskeletal System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>13 13</td>
<td>8 8</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38 4.4</td>
<td>28 5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 2.2</td>
<td>13 0</td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22 10</td>
<td>15 2.6</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>13 0</td>
<td>8 0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>16 2.2</td>
<td>8 0</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>16 8</td>
<td>10 2.6</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>13 2.2</td>
<td>8 0</td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>11 2.2</td>
<td>5 0</td>
</tr>
</tbody>
</table>

### Table 5  Selected Laboratory Abnormalities Worsening from Baseline in Patients with Relapsed or Refractory DLBCL

<table>
<thead>
<tr>
<th>Body System</th>
<th>POLIVY + BR</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>47 7</td>
<td>4 7</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>44 9</td>
<td>26 0</td>
</tr>
<tr>
<td>SGP/T ALT increased</td>
<td>38 0</td>
<td>8 2.6</td>
</tr>
<tr>
<td>SGP/T AST increased</td>
<td>36 0</td>
<td>26 2.6</td>
</tr>
<tr>
<td>Phosphorus decreased</td>
<td>33 7</td>
<td>29 8</td>
</tr>
<tr>
<td>Amilase decreased</td>
<td>24 0</td>
<td>18 2.6</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>24 11</td>
<td>28 5</td>
</tr>
</tbody>
</table>

### Table 6  Selected Laboratory Abnormalities Worsening from Baseline in Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades, %</th>
<th>Grade 3-4, %</th>
<th>All Grades, %</th>
<th>Grade 3-4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>87 87</td>
<td>90 82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>78 61</td>
<td>56 33</td>
<td>53 33</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>78 16</td>
<td>62 10</td>
<td>50 10</td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>83 81</td>
<td>64 26</td>
<td>30 26</td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>47 7</td>
<td>4 7</td>
<td>4 7</td>
<td></td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>44 9</td>
<td>26 0</td>
<td>26 0</td>
<td></td>
</tr>
<tr>
<td>SGP/T ALT increased</td>
<td>38 0</td>
<td>8 2.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>SGP/T AST increased</td>
<td>36 0</td>
<td>26 2.6</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7  Selected Laboratory Abnormalities Worsening from Baseline in Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades, %</th>
<th>Grade 3-4, %</th>
<th>All Grades, %</th>
<th>Grade 3-4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>47 7</td>
<td>4 7</td>
<td>4 7</td>
<td></td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>44 9</td>
<td>26 0</td>
<td>26 0</td>
<td></td>
</tr>
<tr>
<td>SGP/T ALT increased</td>
<td>38 0</td>
<td>8 2.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>SGP/T AST increased</td>
<td>36 0</td>
<td>26 2.6</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

### Table 8  Selected Laboratory Abnormalities Worsening from Baseline in Patients with Relapsed or Refractory DLBCL and ≥5% More in the POLIVY Plus Bendamustine and Rituximab Product Group

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades, %</th>
<th>Grade 3-4, %</th>
<th>All Grades, %</th>
<th>Grade 3-4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>47 7</td>
<td>4 7</td>
<td>4 7</td>
<td></td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>44 9</td>
<td>26 0</td>
<td>26 0</td>
<td></td>
</tr>
<tr>
<td>SGP/T ALT increased</td>
<td>38 0</td>
<td>8 2.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>SGP/T AST increased</td>
<td>36 0</td>
<td>26 2.6</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>
POLIVY® (polatuzumab vedotin-piiq)

Safety was also evaluated in 173 adult patients with relapsed or refractory lymphoma who received POLIVY, bendamustine, and either a rituximab product or obinutuzumab in Study GO29365, including the 45 patients with DLBCL described above. In the expanded safety population, the median age was 66 years (range 27 – 86), 57% were male, 91% had an ECOG performance status of 0-1, and 32% had a history of peripheral neuropathy at baseline. Fatal adverse reactions occurred in 4.6% of recipients of POLIVY within 90 days of last treatment, with infection as a leading cause. Serious adverse reactions occurred in 60%, most often from infection. Table 6 summarizes the most common adverse reactions in the expanded safety population. The overall safety profile was similar to that described above. Data from ≥20% of patients included: dyspnea (19%), pneumonitis (1.7%), arthralgia (7%), weight decrease (10%), transaminase elevation (8%), lipase increase (3.5%).

Table 6 Most Common Adverse Reactions (≥20% Any Grade or ≥5% Grade 3 or Higher) in Recipients of POLIVY and Chemoinmunotherapy for Relapsed or Refractory Lymphoma

<table>
<thead>
<tr>
<th>Adverse Reaction by Body System</th>
<th>POLIVY + Bendamustine + Rituximab Product or Obinutuzumab (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades, (%)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>General Disorders</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Infections</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia</td>
</tr>
</tbody>
</table>

The table includes a combination of grouped and ungrouped terms.

1 Primary prophylaxis with granulocyte colony-stimulating factor was given to 46% of all patients. 
2 Includes 4 events with fatal outcome. 
3 Includes 4 events with fatal outcome. 

Other clinically relevant adverse reactions (>20% any grade included: General Disorders: infusion-related reaction (7%), infection: upper respiratory tract infection (16%), lower respiratory tract infection (10%), herpes virus infection (12%), cytomegalovirus infection (1.2%), Respiratory: dyspnea (15%), pneumonia (1.7%). Nervous system disorders: dizziness (10%). Investigations: weight decrease (10%), transaminase elevation (8%), lipase increase (3.5%), Musculoskeletal disorders: arthralgia (7%), Eye disorders: blurred vision (1.2%).

6.2 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 occurrence of antibodies (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to polatuzumab vedotin-piiq in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Across all arms of Study GO29365, 8/134 (6%) patients tested positive for antibodies against polatuzumab vedotin-piiq in one or more post-baseline time points. Across clinical trials, 14/536 (2.6%) evaluable POLIVY-treated patients tested positive for such antibodies at one or more post-baseline time points. Due to the limited number of patients with antibodies against polatuzumab vedotin-piiq, no conclusions can be drawn concerning the potential effect of immunogenicity on efficacy or safety.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on POLIVY

Strong CYP3A Inhibitors

Concomitant use with a strong CYP3A inhibitor may increase unconjugated MMAE AUC [see Clinical Pharmacology (12.3), which may increase POLIVY toxicities. Monitor patients for signs of toxicity. Strong CYP3A Inducers

Concomitant use with a strong CYP3A inducer may decrease unconjugated MMAE AUC [see Clinical Pharmacology (12.3).]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology (12.2)], POLIVY can cause fetal harm. There are no available data in women on the drug-associated risk. In animal reproduction studies, administration of the small molecule component of POLIVY, MMAE, to pregnant rats during organogenesis at exposures below the clinical exposure at the recommended dose of 1.8 mg/kg POLIVY every 21 days resulted in embryo-fetal mortality and structural abnormalities (see Data). Advise a pregnant woman of the potential 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 2–4% and 15–20%, respectively.

Data

Animal Data

No embryo-fetal development studies in animals have been performed with polatuzumab vedotin-piiq. In an embryo-fetal developmental study in pregnant rats, administration of two intravenous doses of MMAE, the small molecule component of POLIVY, on gestational days 6 and 13 caused embryo-fetal mortality and structural abnormalities, including protruding tongue, malrotated limbs, gastrochisis, and agnathia compared to controls at a dose of 0.2 mg/kg (approximately 0.5-fold the human area under the curve (AUC) at the recommended dose).

8.2 Lactation

Risk Summary

There is no information regarding the presence of polatuzumab vedotin-piiq in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with POLIVY and for at least 4 months after the last dose [see Use in Specific Populations (8.1)].

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating POLIVY [see Use in Specific Populations (8.1)].

Contraception

Females

POLIVY can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the final dose [see Nonclinical Toxicology (13.1)].

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with POLIVY and for at least 5 months after the final dose [see Nonclinical Toxicology (13.1)].

Infertility

Based on findings from animal studies, POLIVY may impair male fertility. The reversibility of this effect is unknown [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Among 173 patients treated with POLIVY in Study GO29365, 85 (55%) were ≥65 years of age. Patients aged ≥65 had a numerically higher incidence of serious adverse reactions (64%) than patients aged <65 (53%). Clinical studies of POLIVY did not include sufficient numbers of patients aged ≤65 to determine whether they respond differently from younger patients.

Avoid the administration of POLIVY in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 x ULN). Patients with moderate or severe hepatic impairment are likely to have increased exposure to MMAE, which may increase the risk of adverse reactions. POLIVY has not been studied in patients with moderate or severe hepatic impairment [see Clinical Pharmacology (12.3) and Warnings and Precautions (5.7)].

7.17 Patient Counseling Information

Peripheral Neuropathy

Advise patients that POLIVY can cause peripheral neuropathy. Advise patients to report to their healthcare provider any numbness or tingling of the hands or feet or any muscle weakness [see Warnings and Precautions (5.1)].

Infection-Related Reactions

Advise patients to contact their healthcare provider if they experience signs and symptoms of infection, including fever, chills, rash or breathing problems within 24 hours of infusion [see Warnings and Precautions (5.2)].

Myelosuppression

Advise patients to report signs or symptoms of bleeding or infection immediately. Advise patients of the need for periodic monitoring of blood counts [see Warnings and Precautions (5.3)].

Infections

Advise patients to contact their healthcare provider if a fever of 38°C (100.4°F) or greater or other evidence of potential infection such as chills, cough, or pain on urination develops. Advise patients of the need for periodic monitoring of blood counts [see Warnings and Precautions (5.4)].

Progressive Multifocal Leukoencephalopathy

Advise patients to seek immediate medical attention for new or changes in neurological symptoms such as confusion, dizziness, or loss of balance; difficulty talking or walking; or changes in vision [see Warnings and Precautions (5.5)].

Tumor Lysis Syndrome

Advise patients to seek immediate medical attention for symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy [see Warnings and Precautions (5.6)].

Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice [see Warnings and Precautions (5.7)].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with POLIVY [see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].

Females and Males of Reproductive Potential

Advise females of reproductive potential, and males with female partners of reproductive potential, to use effective contraception during treatment with POLIVY and for at least 3 months and 5 months after the last dose, respectively [see Use in Specific Populations (8.3)].

Lactation

Advise women not to breastfeed while receiving POLIVY and for at least 2 months after the last dose [see Use in Specific Populations (8.2)].

POLIVY® (polatuzumab vedotin-piiq) M-US-00000111(2.0) 11/20

Manufactured by: Genentech, Inc. June 2019

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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During separate virtual live events, David A. Rizzieri, MD, of Novant Health Cancer Institute, and Grzegorz S. Nowakowski, MD, of Mayo Clinic, discussed later-line options for a patient with diffuse large B-cell lymphoma (DLBCL) with participating physicians.

### EVENT SUMMARY

A 73-year-old woman presented with fever, 7-lb unintentional weight loss, and occasional chest pain. She is married, lives in a rural area, has grown children who live in-state, works part time, and is an avid gardener; she has no family history of cancer. She had a history of hypothyroidism that was controlled with levothyroxine. She had palpable bilateral cervical lymphadenopathy and was negative for hepatitis B, hepatitis C, and HIV.

### CASE SUMMARY

A lymph node biopsy was performed, and immuno-histochemistry panel showed DLBCL. The patient was CD10 and CD20 positive. Fluorescence in sit hybridization assay was negative for rearrangements of *BCL6*, *BCL2*, and *c-MYC.*

A whole-body PET/CT scan showed activity in the colonic wall, with the largest node measuring 3.9 cm and with evidence of subcutaneous tissue involvement. An MRI of the brain showed no evidence of lesions. She received a diagnosis of stage IV DLBCL and intermediate-high-risk disease on the International Prognostic Index. Her ECOG performance status was 0.

The patient received 6 cycles of R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone), which was well tolerated. A PET/CT scan at end of treatment showed a complete response, but 1 year later the patient presented with diffuse lymphadenopathy, which was confirmed by PET CT scan. A biopsy showed relapse of the same DLBCL, and the patient was referred to a transplant center. She completed second-line gemcitabine/oxaliplatin (GemOx) plus rituximab. Post-salvage PET/CT showed no response and a Deauville score of 5. The patient’s ECOG performance status was now 2. She is anxious to initiate another line of therapy.

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate dehydrogenase</td>
<td>300 U/L (280 U/L upper limit)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.8 g/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.3 mg/dL (1.2 mg/dL upper limit)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.7 mg/dL (1.2 mg/dL upper limit)</td>
</tr>
</tbody>
</table>
“What would you most likely recommend for this patient if a clinical trial is not an option?”

**Georgia, North Carolina, South Carolina**
- Tafasitamab + lenalidomide: 73%
- CAR T-cell therapy: 27%

**Connecticut, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont**
- Tafasitamab + lenalidomide: 38%
- CAR T-cell therapy: 12%
- Polatuzumab vedotin ± bendamustine ± rituximab: 12%
- Loncastuximab tesirine: 12%
- Other: 38%

**Total votes:**
- **Georgia, North Carolina, South Carolina:** 11
- **Connecticut, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont:** 8
RIZZIERI: The results are a bit of a mix; chemotherapy, none of us are looking at for the obvious reasons—we’ve already had a couple regimens fail this patient. Tafasitamab [Monjuvi]/lenalidomide [Revlimid] we’re aware of in this situation. Chimeric antigen receptor [CAR] T-cell therapy [could be an option]. With a performance status of 2, she probably couldn’t get through unless it’s from disease and we’d have to find some way to buff this patient up to be a CAR T candidate, but maybe not out of the question down the road. I agree with a nontraditional approach, not just sticking with standard chemotherapy. I agree with the panel.

NOWAKOWSKI: A number of participants voted for CAR T-cell therapy, provided she is agreeable to do that, which I think would be reasonable if she’s willing. A number of other therapies were [voted for], including tafasitamab/lenalidomide, loncastuximab tesirine [Zynlonta], and polatuzumab vedotin [Polivy]/bendamustine/rituximab [Rituxan].

### TABLE. Long-term Results of Tafasitamab/Lenalidomide in the Phase 2 L-MIND Trial

<table>
<thead>
<tr>
<th>NUMBER OF PATIENTS</th>
<th>MEDIAN AGE, YEARS (RANGE)</th>
<th>MEDIAN PRIOR THERAPIES, N (RANGE)</th>
<th>MEDIAN FOLLOW-UP, MONTHS</th>
<th>OBJECTIVE RESPONSE RATE</th>
<th>COMPLETE RESPONSE RATE</th>
<th>MEDIAN DURATION OF RESPONSE, MONTHS</th>
<th>MEDIAN PROGRESSION-FREE SURVIVAL, MONTHS</th>
<th>MEDIAN OVERALL SURVIVAL, MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>72 (41-86)</td>
<td>2 (1-4)</td>
<td>42.7</td>
<td>57.5%</td>
<td>40.0%</td>
<td>43.9</td>
<td>11.6</td>
<td>33.5</td>
</tr>
</tbody>
</table>

For full list of references, visit TargetedOnC.com
A 49-year-old woman presented to her primary care physician with abdominal bloating and nausea. She had a history of mild hypertension. Her mother had died of breast cancer at age 59, and a cousin on her mother’s side had died of ovarian cancer at age 65. A CT scan showed small-volume ascites and bilateral, 8-cm adnexal masses. Her cancer antigen 125 (CA-125) level was 285 U/mL.

She underwent exploratory laparotomy followed by omentectomy, bilateral salpingo-oophorectomy, and resection of pelvic nodules for stage IIIC high-grade serous ovarian cancer. She had optimal cytoreduction with less than 1 cm of residual disease after surgery.

**DISCUSSION QUESTION**
How do you counsel your patients about PARP inhibitor use in the primary maintenance setting?

**WESTIN:** How do you discuss this with patients? What are your goals of therapy, the expected adverse events [AEs], how they’re going to be monitored, duration of therapy, all of that? Dr Mazharuddin, have you prescribed PARP inhibitors for patients in the primary maintenance setting?

**MAZHARUDDIN:** Yes, I have. The goals of therapy are mainly to prevent relapse or recurrence. I explain to them how it works, what to expect as far as AEs and everything, and we go from there. Usually, they’re just happy that it’s an oral treatment.

**ALOBA:** I tell them that it’s a way to try to prevent recurrence. Of course, we monitor the laboratory results a little bit more frequently in the beginning and counsel them about the AEs. We do more frequent follow-ups in the first 3 months. Then, if we know what AEs they’re experiencing from the drug, the visits are going to be less frequent.

**WESTIN:** Yes, I think it’s a good point, and I’d be interested if others have experienced the same. But I do think that many times the bulk of the AEs from PARP inhibition seem to be early on. Once you get your patient on a good strategy for her, then often we can extend those visits out a little bit more.

Dr Reddy, how long do you keep your patients on their up-front PARP inhibitor? What’s your duration of therapy?

**REDDY:** I have used it with a patient for close to 1 year; finally we ended up stopping it because she didn’t like it, or the symptoms. Not so much cytopenias, just the fatigue. ... After 10 or 11 months I ended up stopping it, and she’s still in remission.

**WESTIN:** Good. For a lot of the [Kaplan-Meier] curves, that big first split happens in that first year, maybe pushing in to 18 months. It does beg the question of how long should you
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. 1-3

---

**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.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**
DARZALEX®: 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®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX®.

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® 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® administration. Delayed systemic administration-related reactions have occurred in 1% of patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including chorioidial 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®. Consider administering

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE
Based on the mechanism of action, DARZALEX® and FASPRO® can impact the determination of complete response and of disease the clinical monitoring of endogenous M-protein. This interference Daratumumab is a human immunoglobulin G (IgG) kappa of Complete Response that a patient has received DARZALEX® and DARZALEX antigens in the patient’s serum. The determination of a patient’s ABO persists for up to 6 months after the last daratumumab administration. Daratumumab-mediated positive indirect antiglobulin test may Daratumumab binds to CD38 on red blood cells (RBCs) and DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia DARZALEX® and DARZALEX FASPRO® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets. In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX FASPRO®: Interference With Serological Testing Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX® and DARZALEX FASPRO®.

DARZALEX® and DARZALEX FASPRO®: Interference With Determination of Complete Response Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX FASPRO®: Embryo-Fetal Toxicity Based on the mechanism of action, DARZALEX® and DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX FASPRO® and for 3 months after the last dose. The combination of DARZALEX® or DARZALEX FASPRO® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

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

DARZALEX FASPRO®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, 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-hyaluonidase-fhhj) 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.

cp-248517v3

INDICATIONS AND USAGE
DARZALEX is indicated for the treatment of adult patients with multiple myeloma:
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

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

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

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively.

Nearly all reactions were with the first infusion, with 35% occurring during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms and signs were urticaria, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision [see Adverse Reactions].

When DARZALEX dosing was interrupted in the setting of ASCIT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), on re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCIT. Infusion rate/dilution volume used upon re-initiation was based on the last DARZALEX infusion prior to interruption for ASCIT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCIT were consistent in terms of symptoms and severity (Grade 3 or 4<1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reaction was 88%, with 38% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 2.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion [see Dosage and Administration (2.3) in Full Prescribing Information]. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening reaction (Grade 4) occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion [see Dosage and Administration (2.4) in Full Prescribing Information].

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions [see Dosage and Administration (2.3) in Full Prescribing Information]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease [see Dosage and Administration (2.3) in Full Prescribing Information].

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

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References]. The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX [see Dosage and Administration (2.1) in Full Prescribing Information].

Neutropenia
DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia
DARZALEX may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

Interference with Determination of Complete Response
Daratumumab is a human IgG kappa monoclonal antibody that can be detected in the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein [see Drug Interactions]. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

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

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

ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
• Infusion-related reactions [see Warnings and Precautions].
• Neutropenia [see Warnings and Precautions].
• Thrombocytopenia [see Warnings and Precautions].

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥25%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant
Combination Treatment with Lenalidomide and Dexamethasone (DRd)
The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 46.4 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd) administration. Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).
Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

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

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>Rd (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>13</td>
</tr>
</tbody>
</table>

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

Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (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>Infections</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infectiona</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cougha</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Dyspnear</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spams</td>
<td>26</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>13</td>
</tr>
</tbody>
</table>

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

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

Anaphylactic reaction, IRR (including deaths)

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

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

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.
Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Grade</th>
<th>DRd (N=223)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95</td>
<td>42</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>92</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>13</td>
</tr>
</tbody>
</table>

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

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:

- Newly diagnosed patient studies: D: 2%; V: 1%; DRd: 2%; Rd: 2%; DPd: 2%; DKda: 2%.
- Newly diagnosed patient studies: D: 0%; V: 0%; DRd: 0%; Rd: 0%; DPd: 0%.

Fever, infections reported 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

**DARZALEX® (daratumumab) injection**

**DRUG INTERACTIONS**

**Effects of Daratumumab on Laboratory Tests**

Interference with Indirect Antiglobulin Tests

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

**Interference with Serum Protein Electrophoresis and Immunofixation Tests**

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial ascertainment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

**Clinical Considerations**

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

**Data**

**Animal Data**

Mice that were genetically modified to eliminate all CD38 expression (CD38−/−) showed decreased survival compared to wild-type mice, suggesting that antibodies in breast milk do not enter the neonatal and infant milk. Published data suggests that antibodies in breast milk are not detectable by standard laboratory methods.

**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 milk. Published data suggests that antibodies in breast milk are not detectable by standard laboratory methods.

Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations).

**Pregnancy Testing**

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.
Contraception
Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

Pediatric Use
Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use
Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients [see Adverse Reactions]. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information). Infusion-Related Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing [see Warnings and Precautions].

Neutropenia
Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia
Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding [see Warnings and Precautions].

Interference with Laboratory Tests
Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation
Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again [see Adverse Reactions].

Embryo-Fetal Toxicity
Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

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
U.S. License Number 1864

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cp-271933v2
**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 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) 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, 28% with the second injection and dexamethasone, and progressively 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 include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing. In addition, systemic administration-related reactions, including hypoxia, 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 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: 9 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

**Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis**

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO® in combination with bortezomib, cyclophosphamide 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 III or IV disease were not studied.

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

**Neutropenia**

Daratumumab may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to the manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO® until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

**Thrombocytopenia**

Daratumumab may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to the manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO® until recovery of platelets.

**Embryo-Fetal Toxicity**

Based on the mechanism of action, DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO® may cause 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 FASPRO® and for 3 months after the last dose [see Use in Specific Populations].

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

**Interference with Serological Testing**

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [see References (15)]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions].

Notice blood transfusion centers of this interference with serological testing, and inform blood banks that a patient has received DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX FASPRO® [see Dosage and Administration (2.1) in Full Prescribing Information].

**Interference with Determination of Complete Response**

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein [see Drug Interactions]. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

**ADVERSE REACTIONS**

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Hypersensitivity and Other Administration Reactions [see Warnings and Precautions].
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

**Clinical Trials Experience**

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

**Relapsed/Refractory Multiple Myeloma**

**In Combination with Lenalidomide and Dexamethasone**

The safety of DARZALEX FASPRO® with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADEES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO® 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO®. Serious adverse reactions in ≥5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO® due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO®. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO® in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 83% of patients who received DARZALEX FASPRO®. Adverse reactions requiring dosage interruptions in ≥5% of patients included pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatine increase.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO® in PLEIADEES.
Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionb</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitisd</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

a Fatigue includes asthenia, and fatigue.
b Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

c Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
d Bronchitis includes bronchitis, and bronchitis viral.

e Dysnea includes dysnea, and dysnea 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 sums the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>56</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
<td>52</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>83</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

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

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

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

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were ≥65 years 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 peripheral edema, 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 139 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were ≥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, thirst, 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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continue the therapy. I think the olaparib [Lynparza] studies utilized the PARP inhibitor for 2 years.\textsuperscript{1,2} Niraparib [Zejula] studies have been 3 years.\textsuperscript{3,4} I think being mindful of how long we’re going to keep the patient on is important.

What about dose modifications? When you counsel them, do you talk to them about dose modifications early on, or do you kind of let things happen?

REDDY: In my patient, I didn’t discuss it at the time of starting [maintenance therapy]. I just want to get one thing at a time, say, “This is what it is, let’s get started.” I didn’t discuss the dose [at that point].

MOSCOL: I don’t go into too much detail, either. I just think that when you’re doing the informed consent you need to relay that hematologic toxicity is expected, and eventually we’ll need to hold, or dose reduce, or improve supportive care. It’s overwhelming if you want to go over those details all at once.

WESTIN: I agree with you, Dr Moscol. I don’t like to do a ton of detail. I have started level-setting a little bit with my patients, where I’ll say, “We’re going to start you at this level, but this might not be the right one for you, and we’re going to find your sweet spot of dosing.” And let them know that it’s OK to stop sometimes. I want them to report those AEs. I feel like patients think, “If I’m not getting the maximum dose of chemotherapy, or the maximum dose of this, or if I’m not right on schedule, I’m going to have worse outcomes.” I think letting them know that that’s not the case with these drugs, and sometimes we do need to make adjustments, and it’s OK, is important.

MOSCOL: [Outcomes based on dose reductions] would be very interesting data. In breast cancer, for example, ribociclib [Kisqali] has very interesting data showing that even if you dose reduce by 1 level, the Kaplan–Meier curves looked exactly the same.\textsuperscript{5} So, it was reassuring to know that even when you are cutting back on some of the dose, you still weren’t losing efficacy. I don’t know if they have any of that for PARP inhibitors in ovarian cancer, but that would be quite [helpful].

WESTIN: I’ve seen some early exploratory [analyses] looking at that. The ATHENA trial [NCT03522246] that was just presented at the 2022 American Society of Clinical Oncology Annual Meeting, which was looking at rucaparib [Rubraca], showed dose intensity and benefit with dose reductions.\textsuperscript{6} They saw consistent benefit, even amongst those patients that have a relatively lower dose intensity due to a dose reduction. I think [clinical trial investigators are] starting to realize that we want to see those data, because we know that some of these patients are going to need to be dose reduced. It’s important for us, as we’re counseling those patients.

What about when to take the medications? Obviously, for olaparib, it’s morning and night, so you don’t get to do any manipulation of when patients take medicines. Do you have any specific way you dose niraparib?

KHADE: I typically just counsel the patient on making sure that they take it at the same time every day, whether it’s in the morning or at night.

WESTIN: That’s exactly how I feel, but I will say that if I have patients that are getting some nausea with niraparib, then I will push it to the evening time. They can take an antiemetic and go to bed, and sleep through most of the nausea. That is a strategy that I’ll sometimes use with niraparib, if I’ve got a patient who’s struggling with nausea. It sometimes can help with fatigue, too. If they take it in the evening, they’re not quite as tired during the day. They sleep off the worst of the fatigue.
**DISCUSSION QUESTIONS**

- What are your reactions to the PRIME (NCT03709316) study data?
- Have you used the individualized starting dose of niraparib?
- What AEs do you most frequently observe when using a PARP inhibitor in the primary maintenance setting?

**WESTIN:** How do you feel about these data? I don’t know if you had seen the PRIME data before.\(^4\) Does this make you feel more comfortable potentially starting niraparib at 200 mg for the appropriate patient?

**KHADE:** I haven’t used it with the individualized starting dose, but seeing the data, I would feel comfortable doing that. The [efficacy] was still sufficient, whether you were using the 200-mg or 300-mg dose, when dose reduced for patients with lower body weight or low platelets [From the Data\(^4\)]. I think [thrombocytopenia] is one of the main toxicities that we see, so anything that we use to prevent that, while still maintaining efficacy, is good. So, yes, I would feel comfortable dose reducing.

**WESTIN:** Yes, and it is profound. I just had a [patient] I started on niraparib who went down to a platelet count of 10 x 10\(^9\)/L. When it happens, it catches your eye. So, if there’s any way to reduce the incidence of that, we want to do it. I think we’re getting more and more consistency, that it’s safe and effective.

**REDDY:** A patient I used it with had a large tumor, and I used it based on the platelets and weight. Her [platelet] counts were not an issue, but…she could not tolerate it, because of fatigue. So, I switched her to bevacizumab [Avastin], even though she’s *BRCA*-positive, because she could not tolerate [niraparib].

**WESTIN:** I think our goal, of course, is to try to give the patients the best therapy possible, but tolerance can be an issue. Frequent use of dose interruption and dose reduction is critical, because each patient is going to be fairly unique. I definitely have had some patients—and this goes both ways—that weren’t tolerating one [PARP inhibitor], and I switched to another, just to see if we had a better safety profile, and sometimes you can get away with that, too.

**REDDY:** I don’t know how good bevacizumab maintenance is on *BRCA*-positive patients.

**WESTIN:** Patients with *BRCA*-positive disease do better in general, so there are some data with bevacizumab [suggesting] that they’ll get benefit. You cannot compare cross-trial, but…when you look at median [progression-free survival], the patients definitely go longer without progression when they’re treated with a PARP inhibitor.

What do you think are the most challenging AEs? I’ve heard you talk about [blood cell] counts and a little nausea, and fatigue was another thing that was brought up. Of those things that you’re seeing commonly with these PARP inhibitors, what challenges you the most? What’s making you discontinue?

**MAZHARUDDIN:** I’d say the [blood cell] counts. I can manage nausea with good doses of ondansetron [Zofran]. I’m comfortable with all of those things. But the counts can get a bit difficult, especially with thrombocytopenia.

**WESTIN:** Especially with thrombocytopenia; we can transfuse, but only in desperate times. There’s not a lot you can do medically. I find fatigue the hardest because I don’t have anything good to give them. We don’t have a drug that we can reverse fatigue with, so I feel like fatigue, for me, is the most common cause of needing to dose interrupt and dose reduce.

I think that’s a critical piece. If you just dose reduce when the patient’s having fatigue, it’s going to be hard for her to improve. You want to give them a break and let them recuperate and get back up to their baseline, or at least close to their baseline, before we restart.

I’ve had some patients with—and I’ve seen this reported in a few of the studies—insomnia, some sleep disturbance and things like that. I think that can be a little bit of a struggle, especially if they’re already fatigued, and then they’re not sleeping well. It certainly can be a troublesome one.

**CASE UPDATE**

Germline molecular testing showed the patient was *BRCA* wild-type, and Myriad MyChoice CDx showed homologous recombination deficiency (HRD).

**DISCUSSION QUESTION**

• What would you recommend for this patient at this point?

**WESTIN:** What would you give her for chemotherapy and how do you make that decision?

**ALOBA:** I would give her carboplatin/paclitaxel/bevacizumab, and then I would give her niraparib as maintenance.
WESTIN: So, you would switch her off the bevacizumab and just do the niraparib on its own?

ALOBA: Yes.

WESTIN: I love those PAOLA-1 [NCT02477644] data too, though, [for the] combination [of olaparib and bevacizumab for maintenance]. When you look at the median of time that the patients with HRD stayed on, it's 37 months. Pretty impressive. It's hard to compare it to PRIMA [NCT02655016], though, because it was a bit of a [worse-performing] population, but I do wonder if there's something favoring that combination in that population with HRD. But I often will switch patients to niraparib as well, when they don't want to keep doing injections or infusions and want to just transition to a pill.

Is there anybody you wouldn't use bevacizumab in? Or is there anybody who doesn't use bevacizumab with chemotherapy? I'm a little more selective. I don't use it for everybody. Dr Khade, do you use any bevacizumab in the up-front setting for these patients?

KHADE: Typically not. Typically, we just use the combination of carboplatin/paclitaxel. [Bevacizumab] is an option, I just personally have never used it.

WESTIN: Anybody else use it?

REDDY: Unless there is a true contraindication, my default is with bevacizumab. The only thing is the dose; [for colorectal cancer] it is 5 mg/kg, but we use 15 mg/kg [in ovarian cancer, so I] get a little concerned. I start with 10 mg/kg, and then slowly increase if they tolerate it. It [sometimes] scares me to start at 15 mg/kg.

WESTIN: For this patient specifically, what factors influence your choice of maintenance? Do you think there's a difference in efficacy between these agents? Is that something that you look at, or is every [agent] the same? The data all look pretty consistent, right? The question I have, that we won't have from PAOLA-1, is the combination of olaparib and bevacizumab over just the PARP inhibitor alone. That would [have] been a nice arm to have in that study, to know if bevacizumab adds something for the population that has a BRCA mutation or HRD. That's always a question in my mind.

Are there any AEs that they've had during chemotherapy that will make you go in one direction or the other? Do you consider comorbidities, like hypertension?

MOSCOL: It depends on how bad the hypertension is, right? But certainly with bevacizumab, I'll be a little more concerned if you're trying to use that, you have to watch for nephrotic syndrome [and] edema. If you have a previous history of CAD [coronary artery disease]—this patient is young, but for older patients, I pay attention to it. Stroke, transient ischemic attack, CAD; I would just consider those contraindications.

WESTIN: Yes, I think just to be mindful too, niraparib can cause elevation of blood pressure. It's only in about 20% of patients, but it is something to be mindful of. But, conversely, it has less interaction with other drugs, so if you do have a patient with polypharmacy, sometimes that one is a little bit easier. So those are some of the things that we use in our clinic as we're deciding.
A quick guide to staying healthy for Health Care Professionals

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Participant Perceptions: Treating NSCLC in the Community Setting

M. Sheila Donnelly, MD
Medical Oncologist
Heywood Oncology & Specialty Clinics
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Gardner, MA

Targeted Oncology™: How often do you see patients with lung cancer?

DONNELLY: I see them every week; I have multiple patients on treatment for metastatic disease. I follow a few patients who were treated in the earlier stages and are free of disease. They’re just usual checkups and fortunately they’re doing well. But I have plenty of metastatic patients who are on ongoing therapy and they’re not going to be cured, so we’re hoping for better therapies for them.

How does your practice operate differently in comparison with what was discussed by the Case-Based Roundtable Event participants or in general?

This is for patients with non–small cell lung cancer [NSCLC]. I think I have been prompted to do more next-generation sequencing [NGS] testing. I’m already pretty much up on checkpoint inhibitors because I use them a lot with and without chemotherapy. I have a few patients with mutations that I have on EGFR inhibitors, but I don’t think I’ve done quite as much NGS [utilization] as I should. I realize it doesn’t turn up that many alterations beyond the usual basic panel that the hospital [we work with] uses. They have a panel and I stick with that.

POLLING QUESTION
During a live, virtual event, Woodard, asked participants, “Are you routinely ordering molecular testing for early-stage NSCLC?”

Donnelly answered, “Yes, on most tumors.”

What are some primary considerations or barriers that you have when treating patients at your practice with lung cancer?

Lack of drugs, I suppose. Even with NGS sequencing, you often don’t find mutations that have a drug that can target them. We’re aware of the usual suspects—now there are 10 or 12 [mutations]. But beyond that, we’re still looking to have drug development to match the new findings.

How often do you use adjuvant therapy in patients with NSCLC?

I have 1 patient on osimertinib [Tagrisso] in the adjuvant setting. I had a patient with metastatic disease who passed away who had been on it. And I have 1 patient who’s been on erlotinib [Tarceva] for 5 or 6 years, and she’s still doing well, so I haven’t had to switch her. If she walked in the door today, I would have used osimertinib, but I can’t argue with success.

The double-blind, randomized, phase 3 ADAURA trial (NCT02511106) investigated osimertinib compared with placebo in 682 patients with stage IB to IIIA EGFR-mutated NSCLC. The disease-free survival rate at 24 months in the overall population was 89% with osimertinib vs 52% with placebo (HR, 0.20; 99% CI, 0.14-0.30; P<.001). In December 2020, osimertinib was approved as adjuvant therapy for this patient population based on the ADAURA data.
Amivantamab Shows Strong Efficacy in NSCLC With \textit{EGFR} Exon 20 Insertion

Erminia Massarelli, MD, PhD, MS, discusses the efficacy of the CHRYSLIS trial of amivantamab (Rybrevant) in patients with non–small cell lung cancer and an \textit{EGFR} exon 20 insertion mutation.

View more at: TargetedOnc.com/link/2000

What has your experience been with osimertinib (\textit{From the Data}^{1,2})?

I think it’s very well tolerated. I have limited experience, but this is the adjuvant setting. And the patient who had it for metastatic disease...tolerated it very well and it was a great relief for her. She was an older woman and was not interested in chemotherapy, so I was delighted to have that.

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