Outcomes for heavily pretreated patients with HR+/HER2- metastatic breast cancer (mBC) after endocrine resistance are poor. The median overall survival after single-agent chemotherapies is ~12-18 months.1-5

Gilead Oncology is working tirelessly to ignite innovation after endocrine resistance in HR+/HER2- mBC.

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References:
The Expanding Treatment Paradigm for Urothelial Carcinoma

At an Around the Practice® program hosted by CancerNetwork®, experts spoke about the current treatment paradigms in urothelial carcinoma. The discussion was led by Petros Grivas, MD, PhD, clinical director of the Genitourinary Cancers Program and professor in both the Division of Medical Oncology at the University of Washington School of Medicine and Clinical Research Division at the Fred Hutchinson Cancer Research Center in Seattle.

Panelists included Guru P. Sonpavde, MD, director of genitourinary oncology and Christopher K. Glanz Chair for Bladder Cancer Research at the AdventHealth Cancer Institute in Orlando, Florida; Srikala Sridhar, MD, MSc, FRCP, professor in the Department of Medicine at the University of Toronto and a genitourinary medical oncologist at the Princess Margaret Cancer Centre in Toronto, Ontario; Cora N. Sternberg, MD, FACP, professor of medicine and clinical director of the Englander Institute for Precision Medicine at Weill Cornell Medicine in New York, New York; and Tian Zhang, MD, MHS, assistant professor of medicine at the University of Texas Southwestern Medical Center in Dallas, Texas.
Tian Zhang, MD, MHS, associate professor in the Department of Internal Medicine at The University of Texas Southwestern Medical Center in Dallas.

**Understanding Treatment Paradigms in Urothelial Carcinoma**

**GRIVAS:** What are the guideline-approved therapies for metastatic or advanced urothelial cancer?  
**ZHANG:** Our first-line treatments for metastatic urothelial cancer are still based on chemotherapy. Many of the regimens are cisplatin based. We use either cisplatin with gemcitabine or the 4-drug regimen, MVAC[methotrexate, vinblastine sulfate, doxorubicin, and cisplatin], for active patients with good prognoses and performance statuses. The JAVELIN Bladder 100 trial [NCT02603432] showed that we should use maintenance avelumab [Bavencio] for patients who have at least stable disease or better after chemotherapy.

In the second line, we use immunotherapy regimens—mostly PD-1 or PD-L1 inhibitors—with pembrolizumab [Keytruda] or atezolizumab [Tecentriq]. For patients who are refractory to both chemotherapy and immunotherapy regimens, we have other options. [For example], there is a class of antibody-drug conjugates, including enfortumab vedotin [Padcev] and sacituzumab govotecan [Trodvelv]. We now have erdafitinib [Balversa] for patients with FGFR alterations.

Overall, we’ve come a long way in the past 5 to 7 years in the treatment of metastatic urothelial cancer, and guidelines keep evolving. New trials and new data [are continually creating] new options.

**GRIVAS:** How will new data evolve treatment in the frontline setting?  
**SONPAVDE:** The standard in the frontline setting for most patients was established in the JAVELIN Bladder 100 trial and consists of 4 to 6 cycles of platinum-based chemotherapy followed by maintenance avelumab in patients with stable or responding disease.

However, the most exciting new data concern enfortumab vedotin with pembrolizumab. Enfortumab vedotin, the antibody-drug conjugate targeting NECTIN4 with the [monomethyl auristatin E] toxin, has looked very promising when combined with pembrolizumab in 2 studies so far. In the first-line cisplatin-ineligible advanced urothelial cancer space, enfortumab vedotin with pembrolizumab showed a 73% response rate in a 45-patient phase 1b study. Additionally, we now have [data from] cohort K of the randomized phase 2 EV-103 trial [NCT03288545], in which the combination of enfortumab vedotin with pembrolizumab seemed to show activity consistent with prior data, [resulting in] a 64.5% response rate. The control arm [of enfortumab vedotin alone] also had a robust response rate of approximately 45%, [which is similar to] what was seen before in the second- and third-line spaces. [For this reason], enfortumab vedotin with pembrolizumab looks very interesting in the cisplatin-ineligible space.

Of course, the definitive study will be the phase 3 EV-302 trial [NCT04223856] comparing gemcitabine plus cisplatin with enfortumab vedotin plus pembrolizumab in cisplatin-eligible and -ineligible patients. [Notably], that trial includes [patients treated with] maintenance avelumab in the control arm.

The other trial to watch is CheckMate901 [NCT03036098], which recently [yielded negative results, showing that] ipilimumab [Yervoy] plus nivolumab [Opdivo] could not outperform gemcitabine plus platinum chemotherapy in patients with high PD-L1 expression, regardless of a cisplatin or carboplatin backbone. We’re still waiting for the results of the comparison between gemcitabine/carboplatin vs ipilimumab plus nivolumab in cisplatin-ineligible patients regardless of PD-L1 status. There’s also an interesting substudy comparing gemcitabine/cisplatin vs gemcitabine and cisplatin plus nivolumab. This is a well-powered comparison in the cisplatin cohort only. And as you might remember from the KEYNOTE-361 [NCT02853305] and IMvigor130 tri- als [NCT02807636], the combination of atezolizumab or pembrolizumab with platinum-based chemotherapy looked more promising with a cisplatin backbone. We need to watch this trial because that could also be an option in the first-line treatment setting.

**GRIVAS:** If enfortumab vedotin plus pembrolizumab receives accelerated approval from the FDA, would you stick with the platinum chemotherapy plus avelumab maintenance standard of care and wait for more data from EV-302? Or would you begin using enfortumab vedotin with pembrolizumab?

**SONPAVDE:** I would discuss the data with patients. JAVELIN Bladder 100 included long-term follow-up, and it’s a phase 3 trial showing improved survival. But of course, it’s applicable only to patients with stable or responding disease following platinum-based chemotherapy. Enfortumab vedotin plus pembrolizumab, on the other hand, seemed very robust in the cisplatin-ineligible patient group. A [treatment resulting in a high response rate is attractive] when dealing with patients who are highly symptomatic and whose disease you want to control quickly. [Of course], enfortumab vedotin plus pembrolizumab may not be for everyone, [such as] patients with neuropathy at baseline. However, if you want to control symptomatic disease, enfortumab vedotin plus pembrolizumab may be a very active regimen.

**SRIDHAR:** Ultimately, I prefer to wait for the data from the EV-302 study, as my country requires. [The data regarding] enfortumab vedotin plus pembrolizumab is encouraging and exciting, and the response rates with that combination are starting to challenge those seen with cisplatin, [which is something] we haven’t really seen before. It will also be important to examine which patients are considered cisplatin ineligible and which are not, [as well as] where the line is drawn—because...
if you have a new treatment option, that [line] could change.

**STERNBERG:** A patient of mine with a creatinine clearance of 30 mL/min and widely metastatic disease was treated with enfortumab vedotin plus pembrolizumab, and he’s now completely disease free. The regimen was therefore highly effective in a patient with very low creatinine clearance, which is interesting.

[However], the main problem I have with enfortumab vedotin plus pembrolizumab is that all my patients eventually seem to develop neuropathy. It’s therefore impossible to give this treatment indefinitely. It seems at least as difficult [to tolerate] as cisplatin, or maybe worse, as far as I’m concerned. [For this reason], I prefer to see cutoff at some point, or continue with just the pembrolizumab or something similar.

**ZHANG:** Enfortumab vedotin with pembrolizumab has such high response rates, and it’s the first combination to really challenge chemotherapy in the up-front setting for metastatic disease.

[To speak on] cisplatin eligibility criteria, we often think about the Galsky criteria, a combination of renal function and performance status [that allows] neuropathy and hearing loss to come into play. [This is useful] when deciding which patients can handle cisplatin. We often find overlap between cisplatin-eligible and cisplatin-ineligible populations, so I’m interested to see the data from cohort K to help figure out the right candidates.1

The EV-302 study comparing enfortumab vedotin plus pembrolizumab [with] chemotherapy will set the benchmark for broader ranges of populations.

**GRIVAS:** Do we feel deescalation studies down the road might support shrinking the duration of chemotherapy or enfortumab vedotin?

**STERNBERG:** There are interesting deescalation trials, even with avelumab, [examining the efficacy of] reducing cycles of gemcitabine and platinum-based chemotherapy. [For example], the DISCUS trial [ISRCTN15750433] is comparing 3 vs 6 treatment cycles [of chemotherapy before maintenance in this setting].

Also, regarding maintenance, we’ve only ever studied 2 years of pembrolizumab and indefinite avelumab. We should consider deescalation of these, as well.

Deescalation studies in all tumors should be [thoroughly] considered. We always assume we should give as much therapy as we can, the biggest combinations possible, and the most treatment up front as possible, but I don’t know whether this is always best for our patients.

**GRIVAS:** Could we briefly summarize the JAVELIN Bladder 100 trial?

**SRIDHAR:** JAVELIN Bladder 100 examined approximately 700 patients randomly assigned 1:1 to receive either avelumab or best supportive care [in the maintenance setting following front-line platinum-based chemotherapy]. The avelumab was given at a dose of 10 mg/kg every 2 weeks. As we mentioned earlier, patients were only included if they [were treated previously] with either gemcitabine and either cisplatin or carboplatin. They were required to have undergone 4 to 6 treatment cycles and shown some disease control, either stable disease, partial response, or complete response.2

The randomization occurred after a treatment-free interval of 4 to 10 weeks. The primary end point was overall survival [OS] in both the intention-to-treat population and the PD-L1–high population. The results showed an OS of approximately 21 months with avelumab vs approximately 14 months with best supportive care, which is roughly a 6-month improvement.1 [This was] probably one of the first large phase 3 studies in the frontline setting [to show positive results].

**GRIVAS:** Do you use anything aside from avelumab?

**SONPAVDE:** I stick with avelumab because of those data from JAVELIN Bladder 100 showing an improvement in survival. There was a smaller, randomized phase 2 trial [NCT02500121] of the checkpoint inhibitor pembrolizumab [as maintenance], which examined approximately 50 patients in each arm. The primary end point was PFS [progression-free survival], which was prolonged with pembrolizumab.3 However, this was a phase 2 trial and not powered for survival, so I don’t consider those data standard in the switch-maintenance setting.

**GRIVAS:** Can you briefly comment on the new data from the ATLANTIS trial [ISRCTN25859463] on maintenance with niraparib [Zejula] and cabozantinib [Cabometyx]?

**SONPAVDE:** The ATLANTIS trial is a randomized phase 2 platform trial in the United Kingdom for the switch-maintenance setting examining patients with stable or responding disease after platinum-based chemotherapy. Additionally, within each molecular cohort, there was further randomization to placebo. There was an arm including [patients with] DNA damage repair [DDR] alterations in which niraparib was compared with placebo, and another arm of patients without alterations. They [also examined] cabozantinib vs placebo. [Lastly], there’s an unreported third cohort examining enzalutamide [Xtandi] in patients with androgen receptor and DNA damage alterations. Two of these arms have reported results: the cabozantinib arm and the niraparib arm.

Cabozantinib showed negative results, but [this may have been a consequence of] some negative selection because we don’t know whether patients with DDR alterations are at higher risk.4 Additionally, although niraparib was promising, there wasn’t a good separation of the PFS curves, which was the primary end point.5 This was a well-selected population. We need more data—ideally from a definitive phase 3 trial.
PATIENT CASE 1

- A 63-year-old woman is referred after being evaluated for gross hematuria by her obstetrician-gynecologist.
- Creatinine clearance: 95 mL/min
- Cystoscopy: nodular 6-cm mass along posterior bladder wall
- CT of the chest/abdomen/pelvis demonstrates evidence of pelvic lymphadenopathy and lung metastases.
- Patient has a 20-year smoking history.
- Medical history: mild, controlled congestive obstructive pulmonary disorder; mild hypertension
- ECOG performance status: 1; no significant neuropathy or hearing loss
- PD-L1: combined positive score of 15 by Dako PD-L1 IHC 22C3 pharmDx
- Treatment is initiated with cisplatin/gemcitabine.

GRIVAS: There’s also the ongoing MAIN-CAV trial [NCT05092958] that compares switch-maintenance cabozantinib vs avelumab, correct?

GRIVAS: Would you do anything differently, or would you continue with the described treatment?

STERNBERG: With a younger patient in good shape, I would still use MVAC because it’s stronger than gemcitabine/cisplatin. I see better results with this old-school [treatment]. I do sometimes use gemcitabine/cisplatin, and if the patients are older or have poor creatinine clearance, I will even give them split-dose gemcitabine/cisplatin.

GRIVAS: If you see response or stable disease after 6 cycles on gemcitabine/cisplatin or gemcitabine/cabozantinib, how long do you wait to start avelumab maintenance?

SRIDHAR: That’s a great question. In the study, they examined the treatment-free interval with avelumab. They looked for differences between treatment start points, ranging from 4 to 10 weeks, and didn’t find many. It becomes a discussion with the patient to individualize when they want to start treatment with avelumab. Sometimes they prefer to take a break after chemotherapy, and the data allow that. On average, most of my patients start around 6 weeks after the end of chemotherapy. They finish, recover from the adverse effects, then are ready to get started.

GRIVAS: Looking at these data, do you follow the guideline to continue with avelumab until progression or toxicity? How do you move forward with treatment?

ZHANG: I do usually treat until progression or unacceptable toxicities. Some patients tend to do very well, so they can sustain treatment for several years.

Now at the 2- or 3-year mark, they will sometimes ask whether they can discontinue treatment, and we’ll discuss that. There are not any good prospective discontinuation data, which is certainly something we need. However, it’s reasonable to discontinue if the patient has had an excellent response and wants to stop after 2 years.

GRIVAS: What were the results of the PRESERVE3 trial [NCT04887831]?

SONPAVDE: The PRESERVE3 trial builds on the JAVELIN Bladder 100 paradigm. This is a randomized phase 2 trial examining platinum-based chemotherapy followed by avelumab maintenance with and without trilaciclib [Cosela], which is an intravenous CDK4/6 inhibitor. It’s approved for patients with small cell lung cancer in combination with platinum/etoposide chemotherapy to prevent myelosuppressive complications and has also shown an interesting survival signal in triple-negative breast cancer. The investigators therefore wanted to examine trilaciclib in urothelial carcinoma, because in that space, we have a chance to improve the immune state with avelumab. Data showed trilaciclib can also enhance the patient’s immune state and protect their immune cells by putting them in hematopoietic cell arrest after division. Therefore, trilaciclib could protect the immune cells from chemotherapy and the myeloid cells from the chemotherapy-induced myelotoxicity.

PATIENT CASE 2

- A 73-year-old man presented with dizziness and hematuria.
- CT of the chest/abdomen/pelvis revealed a 3.4-cm mass in the bladder and multiple lung metastases.
- Lung biopsy confirmed stage IV urothelial carcinoma.
- ECOG performance status: 1; no significant neuropathy, patient has grade 3 hearing loss
- Creatinine clearance: 40 mL/min
- Molecular testing: PD-L1 combined positive score, 10; no FGFR2/3 mutation or fusion

GRIVAS: How should this patient be managed?

STERNBERG: This patient has a creatinine clearance of 40 mL/min and hearing loss—at least 2 reasons he would be cisplatin ineligible. For me, this patient has 2 options. [First], he can start with gemcitabine and carboplatin followed by avelumab maintenance. If you think he cannot tolerate chemotherapy, the other
option would be to give him immunotherapy with either pembrolizumab or atezolizumab up front. He’s not eligible for erdafitinib because he doesn’t have an FGFR mutation.

GRIVAS: Would that change if the patient did have an FGFR mutation?

STERNBERG: I wouldn’t give erdafitinib in the frontline setting in any case.

GRIVAS: Would you still give maintenance avelumab regardless of the up-front treatment?

SRIDHAR: Absolutely. JAVELIN Bladder 100 allows us to give maintenance avelumab regardless of chemotherapy regimen, the number of between 4 to 6 and of PD-L1 status. We can begin treatment with avelumab at any time within that treatment-free interval.

GRIVAS: How would you treat a patient who performs very well but then progresses 10 months later on maintenance avelumab?

SONPAVDE: If the patient has an FGFR alteration, erdafitinib and enfortumab vedotin are 2 options. Sacituzumab govitecan is also available for select patients who might not tolerate enfortumab vedotin or erdafitinib.

If the patient doesn’t have an FGFR3 activating mutation or an FGFR2 fusion mutation, erdafitinib is not an option, and enfortumab vedotin is the only drug with phase 3 evidence. However, [other options include] sacituzumab govitecan and docetaxel. Anecdotally, later-line docetaxel does show some activity even after failed treatments with these other drugs.

GRIVAS: If a patient with an FGFR3 mutation progresses on avelumab 10 months later, would erdafitinib or enfortumab work best?

STERNBERG: There are not enough data. Some small studies have suggested treating with erdafitinib first might be better, but [the sample size was small]. I might treat with erdafitinib first, then move on to enfortumab vedotin, but it’s not based on any large study.

GRIVAS: Will toxicity profiles and methods of delivery affect this decision?

ZHANG: Sequential data are hard to find, but patients with FGFR alterations are clearly sensitive to both [erdafitinib and enfortumab vedotin]. I’ve had patients with FGFR alterations who have received enfortumab vedotin [and] FGFR inhibitors. Determining what benefit exposure to these drugs might provide for patients is very important, so I wouldn’t rule out either for patients with FGFR alterations.

GRIVAS: Can you tell us about your study examining enfortumab vedotin plus sacituzumab govitecan?

SONPAVDE: It’s called the DAD trial [NCT04724018], and it’s examining the antibody-drug conjugate enfortumab vedotin plus sacituzumab govitecan. The reasoning was that these drugs target different membrane antigens and have different payload toxins, so there might be synergism without any overlapping toxicities.

We’re also conducting a phase 1 study [NCT04963153] examining enfortumab vedotin in combination with erdafitinib. As mentioned, enfortumab vedotin does show activity in patients with FGFR3 alterations and does not seem to be compromised in retrospective studies. We’ll have to wait and see what the results show.

GRIVAS: Does it make sense to use enfortumab vedotin for a patient with a hemoglobin A1c level of 9.5% and uncontrolled diabetes?

SRIDHAR: That’s a good question. I like the response rates with enfortumab vedotin, and I like involving my endocrinologist, so yes, I would likely use this drug. Uncontrolled diabetes is not a reason to forgo enfortumab vedotin, but it does highlight [a need for caution]. I’ve often seen diabetes [emerge] in patients with no history whatsoever—suddenly you check their blood, and their sugars are increasing. This is an important risk to keep in mind.

With erdafitinib, we must be [watchful for] any new eye, nail, and skin toxicities. The latter may be worse for patients than we assume because they need to use their hands every day.

References


Research into novel therapies for the treatment of hormone receptor (HR)-positive, HER2-negative breast cancer has brought many nonchemotherapeutic treatments to the fore, leaving clinicians with a wide array of options for their patients in this setting.

In a *Between the Lines* segment hosted by CancerNetwork®, Sara M. Tolaney, MD, MPH, chief of the Division of Breast Oncology and associate director of the Susan F. Smith Center for Women’s Cancers at Dana-Farber Cancer Institute, as well as associate professor of medicine at Harvard Medical School in Boston, Massachusetts, sat down with colleagues Martin Dietrich, MD, PhD, and Gregory Vidal, MD, PhD, to discuss optimal sequencing of available agents and their strategies for treating patients whose disease has progressed following standard frontline therapy. Dietrich is a medical oncologist at Florida Cancer Specialists and Research Institute and an assistant professor of internal medicine at the University of Central Florida in Orlando. Vidal is an oncologist at the West Cancer Center and Research Institute in Memphis, Tennessee.

**Treatment Sequencing for HR+/HER2– Breast Cancer**

Early in their discussion, the panelists generally agreed that standard treatment of patients with HR-positive, HER2-negative breast cancer in the frontline setting involves a CDK4/6 inhibitor regimen followed by hormonal therapy, such as an aromatase inhibitor. The tricky part comes when patients progress.

“I’m happy about the opportunity to have additional therapy opportunities, but how to sequence them and what that optimal sequence [looks like] are going to be very challenging,” Dietrich said. “Aside from efficacy, we’re going to be considering adverse effects [AEs], convenience, and the nature of progression.”

Dietrich went on to consider, for instance, a patient with bone-only disease who had a prolonged response to CDK4/6 inhibition, then experienced mild bone progression. In this case, a subsequent line of therapy with an mTOR inhibitor plus fulvestrant or a PI3K inhibitor regimen in a biomarker-driven setting may be appropriate.

Other options include the recently approved fam-trastuzumab deruxtecan-nxki (Enhertu; T-DXd) in patients with unresectable or metastatic breast cancer with low levels of HER2 expression, based on data from the phase 3 DESTINY-Breast04 trial (NCT03734029) that showed a statistically significant improvement in progression-free survival (PFS) with the agent vs physician’s choice of chemotherapy. 1,2 Patients whose tumors do not harbor a traditional biomarker for treatment can receive sacituzumab govitecan-hziy (Trodelvy), which is an antibody-drug conjugate (ADC) that targets the cell surface antigen Trop-2, with evidence of efficacy in this space centering around the TROPiCS-02 trial (NCT03901339). 3
“It’s a paradigm shift in the way we think about targeting cancer, because we’ve always thought about finding an oncogenic driver [first], then figuring out a way to turn off that driver,” Tolaney said. “Now with the examples of T-DXd for HER2-low expression—which is not driving the cancer—and similarly with Trop-2, just knowing there’s a target allows us to have targeted delivery of therapy, which has proven to be so useful in breast cancer.”

Optimal Setting for Sacituzumab Govitecan

Based on early data suggesting sacituzumab govitecan-hziy had efficacy in not only the triple-negative but also the HR-positive breast cancer space, the phase 3 TROPiCS-02 trial was undertaken to confirm its advantage vs physician’s choice of chemotherapy. Patients had HR-positive disease and were heavily pretreated with 2 to 4 lines of prior therapy, including at least 1 each of a taxane, hormonal therapy, and CDK4/6 inhibition. Results showed that among 543 patients randomly assigned in a 1:1 fashion, the blinded independent central review–assessed median PFS was significantly improved with the Tro-2 inhibitor therapy (5.5 months vs 4.0 months, respectively; hazard ratio, 0.66; 95% CI, 0.53-0.83; P = .0003).

Results at the first interim analysis for median overall survival (OS) indicated sacituzumab govitecan-hziy vs standard of care did not result in statistically significant benefit (hazard ratio, 0.84; 95% CI, 0.67-1.06; P = .14). However, results of the second interim analysis were presented at the European Society for Medical Oncology Congress 2022, showing a meaningful improvement in median OS with sacituzumab govitecan-hziy for this patient population at 14.4 months vs 11.2 months, respectively (hazard ratio, 0.79; 95% CI, 0.65-0.96; P = .020).

Looking at the OS and PFS data together, Dietrich pushed for considering sacituzumab govitecan-hziy earlier in the sequence of treatment, as the emergence of statistically significant OS results reassures physicians that this is, in fact, favorable treatment for their patients. “With an OS benefit, I would not reserve it for a late-line setting. It’s an agreeable drug with AEs we can manage,” he said.

Tolaney pointed out the heavily pretreated nature of this population, for which 56% of patients received 3 or more lines of therapy in both the active (58%; n = 159) and control groups (56%; n = 151), which explains why the PFS benefit of approximately 1.5 months may appear underwhelming. “This is in [patients] who have 3 prior lines of chemotherapy, suggesting we do need better therapies here,” Tolaney said. “Seeing this incremental benefit—well, modest at least—is a movement forward.”

Vidal echoed that sentiment by comparing the results seen with sacituzumab govitecan-hziy with T-DXd. “[In] DESTINY-Breast04, patients had to have only 1 or 2 prior chemotherapy agents, whereas TROPiCS-02 was from 2 to 4. It’s a completely different population, [which] may explain some of the differences we see there.”

“Placement and sequence are going to be big discussions. [Only time will tell] how this is going to shake out overall, but I believe earlier usage of sacituzumab govitecan is going to allow the drug to exert a much broader effect than what we’ve seen in TROPiCS-02,” Dietrich said. “Since the design [of the trial] was stacked against the drug in terms of outcomes, I hope we will be able to place it earlier in our clinical setting and make better use of it than we’re seeing right now.”

One interesting consideration that has emerged since T-DXd and sacituzumab govitecan-hziy have shown benefit in an overlapping patient group is the shared characteristics in their mechanism of action, namely their activity against topoisomerase 1 (Topo-1). Tolaney pointed out that TROPiCS-02 was conducted at a time when patients “weren’t receiving prior [agents with] Topo-1 payload and then sequentially going on to receive another Topo-1 payload. In the modern era, this will probably [account for approximately] two-thirds of our patients with [HR]-positive disease and HER2-low expression.”

Vidal continued by pointing out that patients in this setting could present with HER2 status that is 0 or unknown, and rerunning a tissue biopsy could be prohibitive in certain circumstances. In that case, he said he would prefer to go with sacituzumab govitecan-hziy and reiterated the positive OS data. “I fully agree,” Tolaney said. “Target expression comes up a lot, [because] it’s a challenge to figure out who has HER2-low expression or lack of quantitation of HER2 to tease this out.”

Tolaney went on to briefly describe results from the phase 3 ASCENT trial (NCT02574455) of sacituzumab govitecan-hziy in patients with relapsed/refractory metastatic triple-negative breast cancer that showed medium to high expression of Trop-2 conferred greater efficacy of sacituzumab govitecan-hziy, although the trial was not powered to conclude this.\(^3\)

“Understanding the expression would be important. Ultimately, I don’t think it’s going to guide whether we give those patients the drug. We do see even the low [expressors having] some activity, and hopefully we will see the same thing in TROPiCS-02,” Vidal said.

Future Directions

Dietrich said optimal sequencing for these patients with relapsed/refractory HR-positive breast cancer is going to be individualized and will rely on what’s discovered in further research going forward. “The future for breast cancer and ADCs as a whole is bright, because we’re recognizing that we can target these cancers with smaller amounts of chemotherapy and hopefully do less damage to normal cells,” Vidal said. Opening the door to future research efforts may optimize current medications by administering them in combination with other agents.

“There’s just so much we have to learn, but it’s exciting to have these opportunities to improve outcomes for our patients,” Tolaney said.  

**For references visit cancernetwork.com/Breast_BTL_11.22**
The Role of Immunotherapy as a Potential Treatment in Locally Advanced BCC

LIBTAYO® is indicated for the treatment of patients with locally advanced basal cell carcinoma (lABC) previously treated with a hedgehog pathway inhibitor for whom a hedgehog pathway inhibitor is not appropriate.

Please see accompanying full Prescribing Information.

Dr. Karl Lewis, Professor in the Division of Medical Oncology at the University of Colorado, discusses the evolving treatment strategy for locally advanced basal cell carcinoma (BCC) and the role of immunotherapy. This article was sponsored and developed by Regeneron in collaboration with Dr. Lewis.

How often do you see advanced BCC in your practice?
In the United States, more than two million patients are diagnosed with BCC each year and the incidence rates continue to increase over time.1,2 In most cases, BCC can be caught early and cured.3 However, in ~20,000 patients, BCC can progress to an advanced stage where the cancer becomes more difficult to treat and is potentially life-threatening.1,2

While rare, I typically see advanced BCC cases a few times each year.

Why is it important to identify early on if a patient is at risk for advanced BCC?
As with any type of cancer, detecting BCC early is critical to be able to treat the tumor.4

Fortunately, most cases of BCC remain localized and are easily amenable to local intervention, such as excision.1 However, some patients may present with what seems like an innocuous tumor but could already have spread locally under the surface of the skin. In some cases, the disease may appear in compromising places anatomically, such as on or next to the orbit or the nose, making it more difficult to remove.1,2 In these instances, we need to evaluate other forms of treatment.

When are medical oncologists like yourself usually engaged as part of a multidisciplinary team (MDT) to treat someone with advanced BCC?
In some instances, I don’t see patients with advanced BCC until after surgery has been attempted. In some cases, patients may experience disfiguration in the absence of clear margins. In other cases, patients are referred to my practice by other physicians to discuss systemic therapy options as part of their initial work-up.

Advanced BCC is best managed in a multidisciplinary setting that consists of dermatologists, Mohs or head and neck surgeons, as well as radiation and medical oncologists, who can work together to develop the best treatment plan for a particular patient.2

In my experience, the involvement of an MDT can vary based on the referring physician. For cases of advanced BCC, I encourage physicians to involve oncologists early in the treatment process, and over time, I have seen this happen more frequently.

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
How has the treatment landscape for locally advanced BCC evolved in recent years?

Historically, treatment options for patients with locally advanced BCC have been limited to surgery or radiotherapy.1

Some patients with locally advanced BCC may be treated with surgical procedures but determining whether locally advanced BCC is fully resectable is often a challenge.2 If tumors are not completely excised, the risk of disease recurrence is high; alternatively, wide surgical margins can lead to severe disfigurement, loss of function and other detrimental effects.2

Systemic therapies, including hedgehog pathway inhibitors (HHIs), have changed the treatment paradigm for patients with locally advanced BCC.2 However, while HHIs may be effective for many advanced cases, some patients may discontinue HHI therapy due to progressive disease or adverse events and will require another treatment.1,2

In these cases, I believe immunotherapy can play an important role. Specifically, immune checkpoint inhibitors like LIBTAYO, which targets PD-1, may be appropriate in these cases.2

Where does LIBTAYO (cemiplimab-rwlc) fit in the treatment of locally advanced BCC?

In February 2021, LIBTAYO was approved by the U.S. Food and Drug Administration (FDA) as the first treatment indicated for patients with locally advanced BCC previously treated with an HHI or for whom an HHI is not appropriate.4 The approval was based on data from the pivotal Phase 2 trial which included patients with locally advanced BCC after treatment with HHIs.3

What is the recommended dosage for LIBTAYO?

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

Can you elaborate on the dataset that supports the use of LIBTAYO in locally advanced BCC?

LIBTAYO was approved by the FDA based on results from the pivotal, open-label, multicenter, Phase 2, nonrandomized study that included 132 patients, of whom 84 had locally advanced BCC that had progressed on HHI therapy; were intolerant of prior HHI therapy, or had not had an objective response after nine months on HHI therapy.5 Of these 84 patients, 73% of patients discontinued HHI therapy due to disease progression/lack of response and 25% discontinued treatment due to intolerance to HHI therapy.1 Treatment continued until progression of disease, unacceptable toxicity or completion of planned treatment.1

The study excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within five years; history of solid organ transplant; prior treatment with anti–PD-1/PD-L1 therapy or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or Eastern Cooperative Oncology Group Performance Status >2.2

Important Safety Information (continued)

Warnings and Precautions (continued)

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Immune-mediated pneumonitis: LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 56% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.3%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
LIBTAYO was permanently discontinued due to an AR in 13% of patients. Adverse reactions resulting in permanent discontinuation of LIBTAYO in >1.5% (at least two patients) were colitis and general physical health deterioration.5

Dosage delays of LIBTAYO due to an AR occurred in 34% of patients. ARs which required dosage delay in >2% of patients (at least three patients) included blood creatinine increased, diarrhea, colitis, fatigue, headache, pneumonitis and urinary tract infection.7

The most common ARs reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus and upper respiratory tract infection.7 The most common Grade 3 or 4 ARs (≥2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hypokalemia and visual impairment. The most common (>3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia.7 The adverse reactions that occurred in >10% of patients receiving LIBTAYO in Study 1620 can be seen in Table 1.

Table 1 Safety profile of LIBTAYO in Study 16205

<table>
<thead>
<tr>
<th>Adverse reactions (ARs)</th>
<th>All Grades, %</th>
<th>Grades 3-4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>3.8</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>33</td>
<td>1.5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>0.8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>2.3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1.5</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03.

† Fatigue is a composite term that includes fatigue, asthenia, and malaise.5
‡ Musculoskeletal pain is a composite term that includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain.5
§ Rash is a composite term that includes rash maculo-papular, rash, dermatitis, dermatitis acneiform, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, rash erythematous, and urticaria.5
¶ Upper respiratory tract infection is a composite term that includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection.5
# Dyspnea is a composite term that includes dyspnea and dyspnea exertional.5
## Hypertension is a composite term that includes hypertension and hypertensive crisis.5

Important Safety Information (continued)

Warnings and Precautions (continued)

**Severe and Fatal Immune-Mediated Adverse Reactions (continued)**

**Musculoskeletal colitis (continued):** Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

**For hepatitis with no tumor involvement of the liver:** Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
Important Safety Information (continued)

Warnings and Precautions (continued)

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Immune-mediated hepatitis (continued):

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

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

- **Adrenal Insufficiency**: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

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

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

- **Thyroiditis**: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

- **Hyperthyroidism**: Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (126) of patients. Hyperthyroidism resolved in 90% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

- **Hypothyroidism**: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (0.6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

- **Type 1 diabetes mellitus, which can present with diabetic ketoacidosis**: Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin if clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine.

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
Important Safety Information (continued)

Warnings and Precautions (continued)

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Immune-mediated dermatologic adverse reactions (continued): Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.

Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in ≥10 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1-blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

- **Cardiac/vascular:** Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis
- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **Endocrine:** Hypoparathyroidism
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash, and dyspnea. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Complications of allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1-blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

Adverse Reactions

- In the pooled safety analysis of ≥10 patients, the most common adverse reactions (>15%) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea
- In the pooled safety analysis of ≥10 patients, the most common Grade 3-4 laboratory abnormalities (>2%) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia

Use in Specific Populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

Please see accompanying full Prescribing Information.

Indications and Usage

LIBTAYO is indicated for the treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

References:

REGENERON
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A Review of Selinexor Combination Therapies in Relapsed/Refractory Multiple Myeloma

The first-in-class selective inhibitor of nuclear export, or SINE, compound, selinexor (Xpovio), in combination with dexamethasone, was granted FDA approval in 2019 for heavily pretreated patients with multiple myeloma, and subsequent regulatory actions have made this therapy available to a greater share of patients. With more widespread use, additional safety and efficacy data show how this agent will shape administration going forward.

In 2021, a commentary published in Clinical Lymphoma, Myeloma, and Leukemia provided guidance on weekly dosing and supportive care solutions for selinexor in patients with multiple myeloma. In a recent Between the Lines hosted by CancerNetwork®, Joshua Richter, MD, director of multiple myeloma at the Blavatnik Family-Chelsea Medical Center and associate professor of medicine at the Tisch Cancer Institute of Mount Sinai in New York, New York; and Peter Forsberg, MD, associate professor of medicine-hematology at the University of Colorado School of Medicine in Aurora, focused on this commentary and weighed in on how it stands up to their own practice patterns.

Throughout the program, Richter and Forsberg focused on safety and efficacy of selinexor combination regimens, current clinical trials, and ongoing research.

Mechanism of Action
Selinexor helps to block the protein exportin 1 (XPO1), which is responsible for the nuclear export and functional inactivation of tumor suppressor pathways. Blocking of XPO1 results in nuclear preservation and tumor suppressor protein activation; this prevents messenger RNA translation of oncoproteins, in turn leading to apoptosis induction.

“It is definitely a unique mechanism that may translate into a unique effectiveness profile, but it also may have some impact on some of the toxicities and [adverse] effects that we deal with and work through,” Forsberg said.

Richter described the mechanism of action differently, specifically focusing on the role selinexor plays in cell death. He described how malignant cells typically work around programmed apoptosis to allow proliferation and how inhibition of XPO1 can be useful for outsmarting this process.

“When you trigger a cell to undergo apoptosis, you get a signal that travels to the nucleus and then you get a cascade of events—A, B, C, D, and E—that leads to cell death. The cancer cells will get smart and [find a way around that by kicking out C] through these little holes in the nucleus called XPO1…you’ll get A, B, but no C, so the cascade doesn’t follow through, the cell does not die, and the
cancer cell proliferates. What selinexor does is it blocks those XPO1 channels and prevents the cancer cell from kicking out part of that cascade.”

**BOSTON and STOMP Trials**

Two key trials investigating selinexor in patients with relapsed/refractory multiple myeloma were examined in the commentary. One is the phase 1/2 STOMP trial (NCT02343042), which is composed of 11 treatment arms across various combinations containing selinexor plus dexamethasone and including pomalidomide (Pomalyst), bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), carfilzomib (Kyprolis), ixazomib (Ninlaro), and belantamab mafodotin (Blenrep). The other is BOSTON, a phase 3 trial (NCT03110562) analyzing selinexor with bortezomib and dexamethasone (Vd) vs Vd alone.

However, it was the phase 2 STORM study (NCT02336815) that paved the way for use of selinexor in multiple myeloma. This study looked at oral selinexor at 80 mg plus 20 mg of dexamethasone given on days 1 and 3 weekly. Despite robust efficacy, high-dose selinexor totaling 160 mg weekly led to high rates of adverse effects (AEs), leading investigators to explore more optimal dosing strategies to maintain efficacy and reduce toxicity.

**STOMP Trial**

Currently, the most mature data sets for STOMP include those related to selinexor/dexamethasone in combination with pomalidomide, daratumumab, or carfilzomib. Richter and Forsberg began by discussing selinexor/dexamethasone plus pomalidomide for patients with relapsed/refractory multiple myeloma.

Two dosing schedules of selinexor were used for examining selinexor/dexamethasone plus pomalidomide: selinexor either weekly at 60 mg, 80 mg, or 100 mg, or twice weekly at 60 mg or 80 mg; plus escalating doses of pomalidomide at 2 mg, 3 mg, or 4 mg given with the selinexor; and dexamethasone at 20 mg twice weekly or 40 mg each week.

Of the 52 patients in this study, a median of 3 lines of prior therapy were noted, and 84.6% had prior stem cell transplant. The overall response rate (ORR) was 65% with a median progression-free survival (PFS) of 12.3 months and an overall survival (OS) of 19.3 months. The recommended phase 2 dose with this combination was 60 mg of selinexor weekly for 3 of 4 weeks along with 4 mg of pomalidomide, and 40 mg of dexamethasone given orally on a weekly schedule.

“Some of the patients in the selinexor plus pomalidomide arm were already refractory to pomalidomide, and the selinexor resensitized them,” Richter said. Selinexor/dexamethasone plus carfilzomib was the next arm discussed, in which 32 patients were given selinexor at 80 mg or 100 mg, plus carfilzomib at 56 mg/m² or 70 mg/m², plus dexamethasone at 40 mg. The median number of lines of prior therapy in this arm was 4. The ORR was 78.1%: 6.3% of patients had a stringent complete response (CR), 9.4% had a CR, 28.1% had a very good partial response (VGPR), and 34.4% had a PR. The recommended phase 2 dose was 100 mg of selinexor, 16 mg/kg of daratumumab, and 40 mg of dexamethasone, all once weekly. For patients who were daratumumab-naive (n = 19), the ORR was 74% with 5 VGPRs, 9 PRs, and 2 instances of stable disease. Of 2 patients who were refractory to daratumumab, there was 1 patient with progressive disease and 1 with stable disease.

“This update creates a great body of foundational data for us to understand the dosages [of selinexor that were utilized], giving us a dosing structure to begin with. They’re sketching out an efficacy and a safety profile. It’s not a large phase 3 body of data, but it is enough to give us a sense of an active combination strategy in the relapsed/refractory, heavily pretreated [space, more] than some of the other study scenarios,” said Forsberg.

**BOSTON Trial**

BOSTON examined selinexor plus Vd (SVd) vs Vd alone in patients with multiple myeloma who had been treated with 1 to 3 prior lines of therapy. Patients in the active treatment arm were given 100 mg of selinexor once weekly, 1.3 mg/m² of bortezomib once weekly, and 20 mg of dexamethasone twice weekly. Those in the control arm were given bortezomib at 1.3 mg/m² twice per week for the first 24 weeks and once a week thereafter, and 20 mg of dexamethasone 4 times a week for the first 24 weeks and twice a week thereafter.
“[The BOSTON trial] led to an approval [of SVd] in 2020 in patients with 1 or more prior lines of therapy. These patients are not necessarily nearly as heavily pretreated, and [the data also give us] a different insight in terms of the dosing structure,” said Forsberg.

At a median follow-up of 13.2 months for the triplet regimen and 16.5 months for the doublet, the median PFS was 13.93 months (95% CI, 11.73-NE) vs 9.46 months (95% CI, 8.11-10.78), respectively (HR, 0.70; 95% CI, 0.53-0.93; P = .0075).

**Treatment Use and Dosing of Selinexor**

Based on the evidence that has become available since the approval of selinexor/dexamethasone and the STORM trial, once-weekly dosing appears to be a more favorable option when the doublet is combined with other anti-myeloma agents.

“In the original STORM study, we gave selinexor twice weekly at 80 mg. It was more toxic that way, but it had to do all the heavy lifting. When we start combining it with other agents that can share the load, we can get away with once-weekly dosing. For the most part, the maximum tolerated dose in these studies is based off the myelotoxicity of the partner drug,” Richter said.

The participants then shifted the conversation to cover situations in which they like to utilize selinexor for their patients. As evidenced by the data, selinexor/dexamethasone offers better results for patients when coupled with another multiple myeloma backbone therapy vs used alone. However, certain patients have limited treatment options after having received multiple lines of prior therapy.

Richter prefers to turn to selinexor during earlier lines of therapy, preferably in the second line if the first-line treatment has failed.

“If patients receive daratumumab, lenalidomide, and dexamethasone, and they underperform or relapse in a year, then they’re daratumumab refractory, immunomodulatory refractory, and proteasome inhibitor–naïve. I go to [selinexor, bortezomib, and dexamethasone] as a second-line treatment,” Richter said.

However, Forsberg tends to treat patients with selinexor in later lines of therapy, particularly if the patient is on the younger side. “I tend to think about it more in the third line and [later], because my second-line [choices] in the post–lenalidomide relapse [scenario] in younger, robust patients, have currently been leaning toward the CD38 carfilzomib-based combinations,” Forsberg said.

**Toxicity of Selinexor**

In each trial, rates of toxicities correlated with dosing of selinexor. In the STORM trial, the most common grade 3/4 treatment-related AEs (TRAEs) with selinexor at 80 mg twice weekly were thrombocytopenia (53.7%), anemia (29.3%), fatigue (18.7%), and neutropenia (18.7%). In the BOSTON trial, grade 3/4 TRAEs with selinexor at 100 mg once weekly included thrombocytopenia (39%), anemia (16%), and fatigue (13%). In the STOMP trial, grade 3/4 TRAEs with selinexor at 60 mg once weekly were neutropenia (54%), anemia (33.3%), and thrombocytopenia (31.7%).

The commentary also highlighted that nausea was the most common AE experienced by patients overall, but incidence decreased by 50% during cycle 2; after 2 cycles or beyond, more than 90% of patients did not experience it. It was noted that patients should be educated on AEs to expect early on, that they should expect improvement after cycle 1, and that they should not be discouraged and discontinue early.

“My general approach is to try to be more proactive than reactive. An important thing is to get ahead of [AEs], especially any gastrointestinal complications] or nausea. You want to avoid any risk of anticipatory nausea. I tend to be more aggressive early on because you have to worry about it in the first cycle or so,” Richter said.

**Looking Toward the Future**

Moving forward, investigations of selinexor with multiple therapies continue. The results that have been reported so far with a weekly dosing schedule have been positive.

In their closing remarks, Richter and Forsberg discussed some unmet needs in relapsed/refractory multiple myeloma.

“Our toolbox is getting deeper, and when [patients] become refractory to more and more of these agents, what do you do next?” questioned Richter.

“We can hopefully do a lot of great work to build on this robust foundation of myeloma therapies. We know we’re not where we want to be, [and] we need to cross that cure threshold with much more consistency. We just need to keep refining how we can best use the tools that we do have,” Forsberg concluded.

**References**

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You do not need to be registered for the 64th ASH Annual Meeting and Exposition to attend these sessions.
In a recent Face Off program hosted by CancerNetwork®, physicians from Memorial Sloan Kettering Cancer Center (MSKCC) in New York, New York, and Dana-Farber Cancer Institute (DFCI) in Boston, Massachusetts, went head-to-head in a competition-style education program centered on research of treatments for chronic myeloid leukemia (CML). The MSKCC “Yankees” team was led by Michael J. Mauro, MD, leader of the Myeloproliferative Neoplasm Program, while Daniel J. DeAngelo, MD, PhD, chief in the Division of Leukemia at DFCI and professor of medicine at Harvard Medical School, led the opposing “Red Sox” team. Additional commentary during the program was provided by team members Malin Hultcrantz, MD, PhD, assistant attending physician at MSKCC, and Omar Nadeem, MD, clinical director of both the Myeloma Immune Effector Cell Therapy Program and the Center for Prevention of Progression and associate director of Multiple Myeloma Clinical Research Program at DFCI, as well as instructor in medicine at Harvard Medical School.

Each institution reviewed recent studies in CML, allowing the opposing team to ask challenging questions. Each team was awarded points from a live audience after each set of responses, determining a winner at the end of the presentation.

**MSKCC: OPTIC and PACE Trials**

**OPTIC Trial**

The phase 2 OPTIC trial (NCT02467270) evaluated ponatinib (Iclusig) in patients with chronic-phase CML (CP-CML) who were intolerant or resistant to at least 2 prior BCR-ABL1 tyrosine kinase inhibitors (TKIs) or with a BCR-ABL1 T315I mutation. Patients (n = 232) were randomized 1:1:1 and received ponatinib at either 45 mg, 30 mg, or 15 mg once daily. The best response to prior therapy was complete hematologic response or worse in 61% of patients. The primary end point of molecular response, defined as 1% or less of BCR-ABL1 at 12 months, was met in the 45-mg cohort with a rate of 44.1% (98.3% CI, 31.7%-57.0%; P < .017). In the 30-mg and 15-mg cohorts, those rates were 29.0% (98.3% CI, 18.4%-41.6%) and 23.1% (98.3% CI, 13.4%-35.3%), respectively. In the 3 cohorts, the major molecular response (MMR) rates were 34.4%, 24.7%, and 23.1%, with the major cytogenetic response (MCyR) rates being 50.5%, 33.3%, and 43.8% in the 45-mg, 30-mg, and 15-mg cohorts, respectively.
In the 45-mg and 30-mg cohorts, the median progression-free survival (PFS) was not reached, but it was 45.6 months in the 15-mg cohort. At 24 months, the median PFS rates were estimated to be 80%, 76%, and 78% in the 45-mg, 30-mg, and 15-mg cohorts, respectively. The median overall survival (OS) was not reached in any cohort, with OS rates expected to be more than 90% at 24 months in all 3 cohorts.

The most common nonhematologic treatment-emergent adverse effects (TEAEs) were arterial hypertension (28%), headache (18%), and lipase increase (17%) in all cohorts combined. The most common hematologic TEAEs were thrombocytopenia (40%), neutropenia (26%), and anemia (19%).

**PACE Trial**
The phase 2 PACE trial (NCT01207440) investigated ponatinib in patients with Philadelphia chromosome–positive CML or acute lymphoblastic leukemia who were resistant or intolerant to dasatinib (Sprycel) or nilotinib (Tasigna) or who had prior TKI use and a *BCR-ABL1* T315I mutation. The trial aimed to better understand arterial occlusive events (AOEs) that occurred with use of ponatinib. Patients were given ponatinib at 45 mg once daily and could reduce it to 30 mg or 15 mg to manage AEs.

AOEs were categorized as being adjudicated or nonadjudicated if they were recorded as symptoms with a low level of severity and no change in medication. A total of 449 patients were enrolled; 17% had adjudicated AOE and 25% had nonadjudicated AOE. Serious adjudicated vs nonadjudicated AOE occurred in 20% vs 16%, respectively. Baseline risk factors for developing AOE included arterial hypertension and hypercholesterolemia.

Eleven adjudicated AOE were associated with death: 2 cases of cardiac arrest and 1 each of bradyarrhythmia, cardiac failure, intracranial hemorrhage, worsening of congestive heart failure, superior mesenteric artery occlusion, hemorrhagic cerebral infarction, congestive heart failure, ischemic stroke, and acute anterior myocardial infarction. Nine of those 11 patients had a history of cardiovascular events.

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**Yankees at Bat: DFCI Challenges MSKCC**

**DEANGELO:** [In the OPTIC trial], was switching to a lower dose optimal for patients who had a cytogenic remission?

**MAURO:** Most of these patients entered with poor clinical status. Most of them were with CHR [complete hematologic response with their last therapy] or less, meaning that if they had a cytogenic remission it was a significant distance they covered. We know cytogenic remission is a safe remission. However, when I use ponatinib I wait until patients achieve an MMR [to reduce the dose]. While I think it was reasonable in this study—and probably a fairly large number of studies show that cytogenetic remission does offer protection against the risk of progression, which is our most important goal—this is a tough population. I wonder whether waiting until patients have deeper remissions may be a safer strategy.

**NADEEM:** What about the use of antiplatelets or anticoagulants in these trials?

**MAURO:** I’m not aware of any trials that systematically add antiplatelet, lipid-lowering, or other interventions in the setting of CML therapies, or other therapies for that matter, with vascular toxic risk. That’s based on the challenges [presented by] the number of patients you would need to have in a study to prove that your intervention was meaningful. If you look at the cardiovascular literature for primary prevention with aspirin, for example, you need tens of thousands of patients to show a difference, and there aren’t that many outpatients with CML to power a study. The best approach is to make sure these patients with CML have proper cardiovascular risk assessment and risk intervention. Many patients who have dyslipidemia may need aspirin for either primary or secondary prevention and are not on it. I believe that in PACE and other trials, they have looked at patients who are on cardiovascular-protective strategies, and that didn’t necessarily predict AEs.

**HULTCRANTZ:** Is there any overlap between patients with myeloproliferative neoplasms (MPNs) who have a high risk of thrombosis and those with CML who are given aspirin?

**MAURO:** Patients with MPNs have a thrombotic phenotype from the myeloid mutations they carry, which clonal hematopoiesis research has proven is a risk for cardiovascular disease. Our patients all have them. Many of them have driver mutations plus the ones that have been studied. It’s a separate issue. At presentation, patients with CML are at a risk for vascular events, such as priapism ocular disease, and a number of [other] different things that aren’t discussed often because we don’t see them as much. Once you get them on therapy, their platelet function and their bleeding diathesis normalize.
**DFCI: ASCEMBL and PACE/OPTIC Trials**

**ASCEMBL Trial**
The phase 3 ASCEMBL trial (NCT03106779) assessed asciminib (Scemblix) at 40 mg twice daily vs bosutinib (Bosulif) at 500 mg once daily in patients with CP-CML who had been treated with 2 or more TKIs. A total of 223 patients were randomized 2:1 to active or control therapy with a median follow-up of 14.9 months. At baseline, MCyR was observed in 29.3% of patients in the asciminib arm vs 28.9% in the bosutinib arm. After the data analysis cutoff date, treatment was ongoing in 61.8% vs 29.6% of patients, respectively, with 37.6% and 71.1% discontinuing therapy.

The 24-week MMR rate was 25.5% in the asciminib arm and 13.2% in the bosutinib arm, equating to a 12.2% difference between groups after adjusting for baseline MCyR rates (95% CI, 2.19%-22.30%; 2-sided P = .029). The cumulative incidence of MMR at week 24 was 25.0% in the asciminib arm vs 12.0% in the bosutinib arm.

Grade 3 or higher AEs occurred in 50.6% of patients in the asciminib arm vs 60.5% in the bosutinib arm, with treatment-related AEs being reported in 63.5% and 88.2%, respectively. The most common grade 3 or higher AEs leading to treatment discontinuation included thrombocytopenia (3.2%) in patients receiving asciminib and increased alanine aminotransferase (3.9%) in those receiving bosutinib.

**Ponatinib Given After Failure of Second-Generation TKI**
Analysis from Hagop M. Kantarjian, MD, and colleagues focused on cumulative results of safety and efficacy of ponatinib from the PACE (n = 257) and OPTIC (n = 93) trials in patients with CP-CML following failure of prior second-generation TKI treatment. The median follow-up was 57 months in the PACE trial and 32 months in the OPTIC trial, with a median 24-month dose intensity of 30 mg for PACE and 15 mg for OPTIC.

Achievement of less than 1% BCR-ABL1 response occurred in 42% at 12 months, 46% at 24 months, and 47% at 60 months in the PACE trial. In the OPTIC trial, 52% and 57% of patients had the same response at 12 and 24 months, respectively. The 2-year PFS and OS rates in the PACE trial were 68% and 85% respectively. In the OPTIC trial, they were 80% and 91%, respectively.

In patients who received 2 or more TKIs, the 12-month and 24-month rates of response at less than 1% BCR::ABL1 in PACE were 39% and 41%, respectively. In the OPTIC trial, corresponding rates were 55% and 57%, respectively. The 2-year PFS and OS rates were 66% and 88%, respectively, in the PACE trial compared with 73% and 88% in the OPTIC trial.

TEAEs of grade 3/4 occurred at a rate of 81% each in those with 2 or fewer or 3 or more prior TKIs in the PACE trial; in the OPTIC trial, those rates were 67% and 66%, respectively. Grade 3 or 4 treatment-emergent AEs occurred in 12% and 9% of patients in the PACE trial with 2 or fewer or 3 or more prior TKIs vs 5% and 6% in the OPTIC trial.

**Red Sox at the Plate: MSKCC Challenges DFCI**

**MAURO:** In the ASCEMBL trial, if we leveled the playing field between the asciminib and bosutinib doses, what might the AEs look like? **DEANGELO:** We don’t start our patients on 500 mg [of bosutinib]. In fact, we typically ramp up our [doses] to have better tolerability. That wasn’t allowed in this study and that’s a huge criticism. If you had started a patient at 200 mg, 300 mg, or 400 mg vs 500 mg—which is what I usually do—it’s unclear if [the patients] would’ve gotten better tolerability. More is not always better in all of these drugs. As you know, imatinib [Gleevec] may be the exception, as the TKI trial showed, but almost all the FDA-approved drugs have the option to dose reduce. I do think the tolerability may have suffered in this trial, but I don’t think the conclusion should [dissuade clinicians from using] asciminib—at least in patients who have failed second-generation TKI, especially multiple second-generation TKIs—is better than moving on to a third like bosutinib.

**MAURO:** Can you discuss the 6-month MMR in the ASCEMBL trial? Was it appropriate or should it have been a later time point? **DEANGELO:** In your presentation last year, you showed the longer-term data of 48 weeks and 96 weeks, which were the secondary end points and are important. There are fewer patients on the bosutinib arm out that far. Not only do patients continue to respond to asciminib, but the difference between the responses with asciminib vs bosutinib in this case increased. You’re saying 24 weeks may not be the right thing, although you can argue that maybe 48 weeks is a better end point than 24 weeks. Undoubtedly, faster responders do better than slower responders. The data that I showed took
that out to 96 weeks and supported that.**MAURO:** Is it fair to compare ponatinib vs asciminib in these populations?**DEANGELO:** No—that’s why you’re never supposed to compare studies, because of different patient populations and different eras. It is important to note that we have 5-year data in the PACE trial and we have long-term data in the OPTIC trial. We don’t have long-term trial data in the ASCEMBL study. Long-term follow-up is going to be important. In the ASCEMBL study, so few patients are left on the control arm. If you look at just the asciminib arm [efficacy] looks comparable, but we have longer data with the ponatinib arm. There’s something to be said about a study that can go out 5 years and show patients who responded, and these were heavily pretreated patients with a response that is durable, and we just don’t have the same luxury of data on the ASCEMBL study.

Stay tuned for our next installment of Face Off, where the MSKCC Yankees and the DFCI Red Sox will debate multiple myeloma and the winner will be determined.

**References**

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