Fixed-Duration Therapy Struggles to Find Footing Across Tumor Types

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CAR-T, chimeric antigen receptor T cell; PD-1, programmed cell death-1; TKI, tyrosine kinase inhibitor.
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STRATEGIC ALLIANCE
Fixed-Duration Therapy Struggles to Find Footing Across Tumor Types

by MEIR RINDE

Long-term and retrospective results of studies in hematologic malignancies have carved out roles for fixed-duration therapies among several disease states. The benefits of the therapy include less out-of-pocket spend for long-term agents and reduced adverse effects. However, leveraging time-bound therapeutic regimens has failed to gain traction across several tumor types.
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OncLive® Partnerships Fuel the Delivery of Topline Information

EVERY ISSUE OF ONCOLOGYLIVE® the partner perspectives section highlights contributions from the leaders at top institutions. These submissions are from member institutions of the OncLive® Strategic Alliance Partnership (SAP) program, a nonmone-
tary, nonexclusive, collaboration tool that aligns the print, digital, and event tactics to elevate our partner’s key objectives.

OncLive® is proud to partner with 96 leading cancer centers across the country to collaborate on content that provides oncology professionals with the resources and information they need to give the best patient care.

The Partner Perspectives section of OncologyLive® provides the platform for investigators to reflect on the latest research, provide insight to the challenges facing their practice, and highlight programs and initiatives at their institution. Thus far in 2022, OncologyLive® has featured updates in robotic navigational bronchoscopy for early-stage lung cancer from Roswell Park Comprehensive Cancer Center, data from novel risk- and response-adapted strategies out of the University of Wisconsin Carbone Cancer Center, reflections on the state of treatment options for the treatment of amyloid light-chain amyloidosis from the Cleveland Clinic, and a look at prognostic tactics for advanced head and neck cancer recurrence from investigators at the Montefiore Einstein Cancer Center.

In this issue’s partner perspective, Shonali Midha, MD; Omar Nadeem, MD; and Irene Ghobrial, MD, of Dana-Farber Cancer Institute in Boston, Massachusetts, explore the hurdles facing investigators to apply early intervention tactics in multiple myeloma. Without an established screening protocol in place for most hematologic malignan-
cies, the authors unpack the latest data from the 63rd American Society of Hematology Annual Meeting and Exposition which underscore the growing focus on advancing methods of detection and improving our understanding of the genomic, genetic, and epigenetic factors that govern progression and therapeutic resistance. For more on this topic, see PAGE 56.

Our partners are also instrumental for providing a voice in the field at major meet-
ings. During the 2022 Genitourinary Cancers Symposium, OncLive® spoke with lead authors on several studies to gather their top takeaways from the pivotal data presentations. This included Toni Choueiri, MD, director of the Lank Center for Genitourinary Oncology, director of the Kidney Cancer Center, and senior physician at Dana-Farber Cancer Institute on the updated 30-month results of the phase 3 KEYNOTE-564 trial (NCT03142334) in renal cell carcinoma (RCC). For coverage of the meeting, turn to PAGE 24 and see the Meeting Reporter included with this issue.

For more information on the program and to hear from our partners, visit onclive.com/sap-partner or contact our OncLive® Strategic Alliance Partnership Coordinator, Noelle Stango (nstango@mjhlifesciences.com).

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IN A PROVOCATIVE COMMENTARY entitled “Scientists: When Talking to the Public, Please Speak Plainly” that was published in Scientific American, Naomi Oreskes, PhD, chastises the scientific community for frequently “speaking in code.” Language used by individuals working in a specific area may be understood but that may not be the case for the broader scientific community and certainly not the general public. This is potentially problematic as the public becomes increasingly exposed to scientific discourse and publications.

Oreskes, the Henry Charles Lea Professor of the History of Science at Harvard University in Boston, Massachusetts, gives several examples of how terminology may be confusing and lead to incorrect and even dangerous interpretations by nonexperts. She notes, “Studies show that alien terms are, in fact, alienating; they confuse [individuals] and make them feel excluded. One study showed that even when participants were given definitions for the terms being used, jargon-laden materials make them less likely to identify with the scientific community and decreased their overall interest in the subject. In plain words: jargon turns people off…. If scientists could speak plainly, it would help us understand their claims and better appreciate their work.”

WHAT DOES IT MEAN?

An unfortunate real-world example of this concern is the FDA regulatory jargon related to the approval process and labeling of COVID-19 vaccines. Despite the unquestionably clearly documented safety and efficacy of several commercially available COVID-19 vaccine products, the FDA just recently granted “full approval” to the agents. Unfortunately, it must be asked: What does the use of the term full approval signify to the vaccine-hesitant or vaccine-resistant populations? They may raise questions such as: Was the vaccine—administered these many months to billions of individuals—just part of a worldwide experiment prior to this now-stated stamp of approval? Why not use terminology that provides reassurance to the public rather than information that leads to the questioning of government and public health officials who have been struggling to encourage vaccination?

In the oncology arena, terms frequently used by investigators in clinical trials—and subsequently in clinical practice—to describe the goals of therapy can lead to questions from patients and their families. At times it may even be asked if the treating physician will be able to provide a satisfactory explanation.

Consider, for example, the increasingly used term maintenance therapy: What is the basic meaning of this therapeutic strategy? Does the meaning apply to all settings where the oncology community states a maintenance strategy is being employed?

It is important to understand the history of anticancer drug therapy and specifically the administration of cytotoxic drugs. Until relatively recently, the duration of drug therapy delivery in the management of advanced or metastatic cancers was quite limited. This was because the known serious toxicity profiles of available clinically useful agents prevented extended use. Such adverse effects (AEs) included the risk of intense emesis (nausea, vomiting, or both), peripheral neuropathy (short term and persistent), life-threatening cardiotoxicity, and debilitating fatigue. Furthermore, the risks of such events in most circumstances worsened as therapy was prolonged.

In general, it was unlikely that most patients would be able to tolerate more than approximately 6 to 9 cycles of these agents delivered every 3 or 4 weeks. These limitations of treatment duration were particularly relevant for platinum agents (cisplatin, carboplatin, oxaliplatin), doxorubicin, and the taxanes (paclitaxel, docetaxel), which historically are among the most effective cytotoxic agents in many solid tumor types.
Therefore, investigators advanced the idea that following the delivery of a limited number of courses of an alternative, less-toxic approach might be substituted to maintain an observed response. It is not difficult to explain this laudable but understandably narrow aim. However, what else does the term maintenance imply?

Let’s consider that a clinical goal is to administer treatment to cure a patient’s illness, improve overall survival, or, more modestly, improve time to subsequent symptomatic disease progression without meaningfully affecting overall survival. Assuming there is an acceptable profile for AEs, is the intent to continue maintenance indefinitely, perhaps for the remainder of the patient’s life? Or is it to deliver therapy for a defined period and then discontinue treatment until evidence of disease progression?

It is relevant to note the potential heterogeneity of possible responses to these questions in contrast with a somewhat related older term, consolidation, which is used in hematologic malignancies. When employing a consolidation approach, once initial therapy is discontinued, patients receive 1 or 2 cycles of intensive therapy delivered with the very specific goal of consolidating the response and curving the malignancy. The AEs observed from the consolidative regimen may be even greater than the initial regimen, but the duration of such therapy will be limited and has the clear goal of increasing the opportunity for cure.

The unambiguous aim of this therapy will almost certainly not be conveyed through the term maintenance. Consider 2 examples that using “maintenance therapy” implies for anticipated outcomes, specifically, the observed outcomes from using one of several PARP inhibitors in the first-line treatment of patients with BRCA mutation-positive advanced epithelial ovarian cancer vs those with BRCA mutation-positive metastatic pancreatic cancer. In pancreatic cancer, unfortunately, the likely duration of maintenance treatment will be limited. As a result, the use of traditional cytotoxic regimens and continuing therapy until disease progression or unacceptable AEs will generally apply to this patient population. However, investigators have observed that maintenance therapy used in the first line for patients with BRCA mutation-positive advanced epithelial ovarian cancer remarkably extended progression-free survival.

Further, the potential benefits of maintenance therapy in ovarian cancer vary based on the prior status of the malignancy (primary, first recurrence, second recurrence, etc) and, in the case of PARP inhibitors, the presence or absence of BRCA mutations or molecular evidence of homologous recombination deficiency or proficiency.

As a result, in the case of ovarian cancer where extended progression-free survival has been observed, it is necessary to ask the questions previously posed in this commentary. Should treatment be continued indefinitely for years if AEs are minimal or tolerable? Is continued treatment simply suppressing cancer for as long as it is delivered, or can extended delivery actually cure the condition? Answers to these questions are eagerly awaited.

Investigators should look at these 2 uses of maintenance therapy and determine if the definition of the term is applicable for similar treatments with different goals among both populations.

REFERENCES
DEEP DIVE

**Cisplatin-Induced Hearing Loss in Pediatric Patients**

Bruce Carleton, PharmD, FCP, FISPE, of the University of British Columbia in Vancouver, and his colleagues investigated cisplatin-induced hearing loss (CIHL) incidence in pediatric patients. Although the mechanism of action requires further investigation, their study results indicated close audiological monitoring is necessary after each cisplatin cycle for patients 5 years or younger. Specifically, at 1 year, CIHL was 61% (95% CI, 53%-69%) for patients 5 years or younger (n = 140) compared with 48% (95% CI, 37%-62%) for patients over the age of 5 (n = 228; P < .001). Parents and providers may not have to accept the risk of hearing loss to preserve survival in the future, Carleton said.

+ TO WATCH, VISIT bit.ly/3p3vszK.

INSIDE THE PRACTICE

**“Go To Know” Campaign for Colorectal Cancer Screenings**

African American patients are 40% more likely to get colon cancer and 20% more likely to die from colon cancer than non-Hispanic White patients, according to Ron Brooks, MD, FACP, of Independence Blue Cross in Philadelphia, Pennsylvania. This significant health equity issue was the premise behind Brooks’ health awareness campaign, “Go To Know,” which was launched in 2021. Brooks and his team seek to increase the rate of colon cancer screenings among African American patients by providing free fecal immunochemical tests. Brooks said the goal is that this campaign will trickle into screenings for other diseases, such as breast cancer and diabetes.

+ TO WATCH, VISIT bit.ly/3LSS5AB.

SECOND OPINION

**Cost of Care in Non–Small Cell Lung Cancer**

Immunotherapy has shown significant benefit as a frontline treatment in patients with non–small cell lung cancer. But does the durability of response offset the cost of treatment? Rachel E. Sanborn, MD, of Providence Cancer Institute in Portland, Oregon, noted that health care systems and insurance providers in the US negotiate the cost of drugs differently. This leads to a significant price variation between regions and among individual patients an oncologist will treat. Yusuf A. Gaffar, MD, of Maryland Oncology Hematology in Columbia, resolved that available data on the duration of such treatments can provide a more accurate quote for the total cost of care.

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**FoundationOne CDx Gains Indication as Pembrolizumab Companion in MSI-H Solid Tumors**

The FDA has approved an additional indication for FoundationOne CDx as a companion diagnostic to identify patients with microsatellite instability-high (MSI-H) solid tumors that may be candidates to receive and derive benefit from pembrolizumab (Keytruda). This approval provides an assay that complements the 2017 accelerated approval of pembrolizumab for use in adult and pediatric patients with unresectable or metastatic, MSI-H or mismatch repair-deficient solid tumors that have progressed following prior treatment and who do not have satisfactory alternative treatment options.

The tissue-based genomic profiling test was designed to detect substitutions, insertions, and deletion alterations, and copy number alterations in a total of 324 genes and select gene rearrangements. The test also identifies tumor mutational burden (TMB) and MSI through the utilization of DNA isolated from formalin-fixed paraffin-embedded tumor tissue specimens. FoundationOne CDx has an additional approval with pembrolizumab for the identification of patients with TMB-high solid tumors.

TO READ MORE, VISIT bit.ly/3s826SK.

**Decision Deadline Is Set for Liso-cel in Second-Line Relapsed, Refractory LBCL**

The FDA has accepted and granted priority review to a supplemental biologics license application (sBLA) seeking the approval of lisocabtagene maraleucel (Breyanzi; liso-cel) for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) in whom frontline therapy has failed. Under the Prescription Drug User Fee Act, the regulatory agency is expected to decide on the sBLA by June 24, 2022.

The application is based on data from the phase 3 TRANSFORM trial (NCT03575351). At a median follow-up of 6.2 months, the median event-free survival (EFS) in those who had received liso-cel (n = 92) was 10.1 months (95% CI, 6.1-not reached) vs 2.3 months (95% CI, 2.2-4.3) among those who had received standard salvage chemotherapy followed by high-dose chemotherapy plus autologous hematopoietic stem cell transplant (n = 92; HR, 0.349; 95% CI, 0.229-0.530; P < .0001).

Moreover, the 6-month EFS rates with the chimeric antigen receptor T-cell therapy and the standard-of-care treatment were 63.3% (95% CI, 52.0%-74.7%) and 33.4% (95% CI, 23.0%-43.8%), respectively. At 12 months, the EFS rates were 44.5% (95% CI, 29.4%-59.6%) and 23.7% (95% CI, 13.4%-34.1%) in the investigative and control arms, respectively.

TO READ MORE, VISIT bit.ly/3v7Irnu.

**Adagrasib Undergoes Evaluation for Previously Treated KRAS G12C-Mutated NSCLC**

The FDA has accepted a new drug application (NDA) for adagrasib for the treatment of patients with non–small cell lung cancer (NSCLC) whose tumors harbor a KRAS G12C mutation and who have previously received at least 1 prior systemic therapy. A decision is expected by December 14, 2022.

The application is supported by findings from the phase 2 registration-enabling cohort (n = 19) of the KRYS1AL-1 trial (NCT035785249). At a median follow-up of 9 months, patients who received a twice-daily dose of 600 mg achieved an objective response rate of 43% and a disease control rate of 80%, based on central independent review.

Notably, 98.3% of patients received adagrasib after having received chemotherapy and immunotherapy. The safety and tolerability of the agent proved consistent with what has previously been reported on its use in those with advanced NSCLC.

Detailed results from the cohort supporting the NDA are anticipated to be shared at a medical meeting in the first half of 2022. Investigators are evaluating adagrasib in combination with docetaxel in patients with advanced NSCLC whose tumors harbor a KRAS G12C mutation in the phase 3 KRYS1AL-12 trial (NCT04685135).

TO READ MORE, VISIT bit.ly/3s826SK.

**Califf Is Confirmed as FDA Commissioner**

The US Senate confirmed Robert M. Califf, MD, a prominent cardiologist and expert in clinical trials, as the latest FDA commissioner in a 50-46 vote on February 15, 2022. Prior to Califf’s appointment, the regulatory agency had been without a permanent leader for more than a year.

The confirmation marks Califf’s return to the FDA. He previously served as the FDA’s deputy commissioner for medical products and tobacco from February 2015 to February 2016 and was commissioner from 2016 to 2017. More recently, he was a senior adviser at Alphabet, contributing to strategy and policy for its health subsidiaries Verily Life Sciences and Google Health.

Previously, Califf held an appointment as a professor of medicine (cardiology) at Duke University School of Medicine and was founding director of the Duke Clinical Research Institute in Durham, North Carolina. Also at Duke, he led the Clinical Trials Transformation Initiative, a public-private partnership cofounded by the FDA and the university. He was the principal investigator for the university’s Clinical and Translational Science Award and the NIH Health Care Systems Research Collaboratory coordinating center, as well.

TO READ MORE, VISIT bit.ly/3H81ikY.
IS MYELOFIBROSIS TREATMENT ILL-FITTED TO PATIENT NEEDS?

Not all treatments are sufficient for all patients — which leaves them with less than optimal outcomes.¹ New approaches must be pursued to manage a fuller range of signs and symptoms in myelofibrosis.

TO LEARN MORE, VISIT MYELOFIBROSISINSIGHTS.COM

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Drug Spotlight

CILTACABTAGENE AUTOLEUCEL SUSPENSION FOR INTRAVENOUS SUSPENSION (CARVYKTI)

THE FDA HAS APPROVED cilta-cel, a single infusion at a target dose of 0.75 × 10⁶ CAR-positive viable T cells/kg (range, 0.5 × 10⁶ to 1.0 × 10⁶).

Five to 7 days following the initiation of lymphodepletion, patients were administered cyclophosphamide at 300 mg/m² and fludarabine at 30 mg/m², both administered daily for 3 days.

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Cilta-cel is unique in that it has 2 single-domain binding antibodies that bind to BCMA and the intracellular signaling domain, 4-1BB costimulatory domain, and a CD3 (signaling cytoplasmic domain),” Thomas G. Martin, MD, said in an interview with OncologyLive®. “CARTITUDE-1 evaluated patients who had relapsed or refractory myeloma [and who had] received [a median of] 6 prior lines of therapy; 88% of patients were triple-class refractory. This is a heavily pretreated population.

The study was designed to prove this single infusion of cilta-cel could provide deep and durable responses in this relapse or refractory patient population.” Martin is a clinical professor of medicine in the Adult Leukemia and Bone Marrow Transplantation Program, associate director of the Myeloma Program at the University of California, San Francisco (UCSF), clinical research director of hematologic malignancies at the UCSF Helen Diller Family Comprehensive Cancer Center, and director of the unrelated donor transplantation programs for adults at the UCSF Medical Center.

The single-arm, open-label, phase 1b/2 trial enrolled patients with multiple myeloma who were at least 18 years of age, had measurable disease at screening, and an ECOG performance status of 0 or 1.

Patients needed to have previously received 3 or more prior lines of therapy or become double refractory to a proteasome inhibitor and an immunomodulatory drug and have received a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 antibody, with documented progressive disease.

Patients’ blood was apheresed in accordance with institutional standards.

The median time from leukapheresis to product availability was 32 days (range, 27-66). Between apheresis and CAR T-cell infusion, patients were permitted to receive bridging therapy if clinically indicated. After the successful manufacturing of cilta-cel, patients underwent lymphodepletion with cyclophosphamide at 300 mg/m² and fludarabine at 30 mg/m², both administered daily for 3 days.

Five to 7 days following the initiation of lymphodepletion, patients were administered a single infusion at a target dose of 0.75 × 10⁶ CAR-positive viable T cells/kg (range, 0.5 × 10⁶ to 1.0 × 10⁶).

The median age of patients was 61.0 years (interquartile range [IQR], 56.0-68.0), the median time from diagnosis was 5.9 years (IQR, 4.4-8.4), and patients received a median of 6 prior therapies (IQR, 4.0-8.9).

Eighty-four percent of patients had been exposed to 5 drugs. Moreover, 84% were refractory to pomalidomide (Pomalyst), 65% to carfilzomib (Kyprolis), and 99% to anti-CD38 antibody treatment. Eighty-eight percent of patients were triple-class refractory, 42% were penta-drug refractory, and 99% were refractory to their last line of therapy received.

The primary end point of the phase 2 portion was ORR. Secondary end points in both phases included sCR, complete response, very good partial response (VGPR), DOR, rate of minimal residual disease negativity, progression-free survival (PFS), and overall survival (OS).

Martin presented updated data at the 63rd American Society of Hematology Annual Meeting and Exposition. At a median follow-up of 2 years, the sCR increased to 82.5% with a VGPR or better of 94.9%. The median time to first response was 1 month (range, 0.9-10.7), with a median time to best response of 2.6 months (range, 0.9-17.8).

Among all treated patients, the median PFS was not reached (NR; 95% CI, 25.5-not estimable [NE]), with a 2-year PFS rate of 71.0% (95% CI, 57.6%-80.9%). The median OS was NR (95% CI, 27.2-NE), with a 2-year OS rate of 74.0% (95% CI, 61.9%-82.7%). Among those who achieved sCR (n = 80), the median PFS was NR (95% CI, 22.8-NE), with a 2-year PFS rate of 60.5% (95% CI, 48.5%-70.4%). Results also demonstrated how minimal residual disease (MRD) negativity, when evaluated at a threshold of 10⁻⁶, correlated with survival.

“Sixty-one percent of patients were evaluable for MRD negativity, and 92% achieved MRD negativity,” Martin said. “For those who had MRD negativity sustained for 6 months or more [n = 30], the 2-year PFS rate was 91%. For those who had sustained MRD negativity for 12 months or more [n = 18], the 2-year PFS rate was 100% in both of those groups. At 2 years, the OS rate was also 100%, which is pretty amazing.”

Further efficacy data showed a benefit across populations. This included among patients 65 years and older (n = 35), 8 of whom were 75 years and older. The ORR was 97.1% (95% CI, 85.1%-99.9%), and the MRD negativity rate was 91.3% (95% CI, 72%-98.9%). “One of the important parts of this [study] is we [must] further [evaluate] those populations to try to see whether we can pick out biomarkers or characteristics of these patients that might predispose patients to having such great responses,” Martin said.

Regarding safety, all patients experienced toxicities, including grade 3 or 4 AEs. The most common AEs reported were hematologic in nature. Grade 3 or 4 hematologic toxicities included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). Those who had grade 3 or 4 cytokine events following day 1 of CAR T-cell infusion recovered to grade 2 or less by day 30 for lymphopenia (88%), neutropenia (70%), and thrombocytopenia (59%).

Cilta-cel is available through the restricted Carvykti Risk Evaluation and Mitigation Strategy Program. There is a boxed warning for this treatment regarding cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, Parkinsonism and Guillain-Barré syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged and/or recurrent cytopenias.

“The future is bright for all patients with relapsed or refractory multiple myeloma, and it includes CAR T-cell therapeutics. But there are [several] other therapeutic strategies being investigated, including the T-cell engaging antibodies, for which data look exciting,” Martin said.

REFERENCES


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**FDA approval—February 28, 2022**

The FDA approves ciltacabtagene autoleucel (cilta-cel; Carvykti) for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior or lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

**Mechanism of action**
- Cilta-cel is a B-cell maturation agent (BCMA)-directed, genetically modified autologous T-cell immunotherapy, featuring 2 BCMA-targeting single-domain antibodies—a 4-1BB costimulatory domain and a CD3ζ signaling cytoplasmic domain—designed to confer high avidity against human BCMA.

**How supplied**
- Single dose for infusion, containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells in 1 infusion bag

**Dose**
- The recommended dose range is 0.5-1.0 × 10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1.0 × 10^8 CAR-positive viable T cells per single infusion

**Company:** Janssen Biotech, Inc

**PIVOTAL CLINICAL TRIAL**

CARTITUDE-1 (NCT03548207) was an open-label, single-arm, multicenter trial in adult patients with relapsed or refractory multiple myeloma, who received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

**Efficacy Results in CARTITUDE-1**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cilta-cel (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)*</td>
<td>97.9% (92.7%-99.7%)</td>
</tr>
<tr>
<td>sCR (95% CI)</td>
<td>78.4% (68.8%-86.1%)</td>
</tr>
<tr>
<td>VGPR (95% CI)</td>
<td>16.5% (9.7%-25.4%)</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>3.1% (0.6%-8.8%)</td>
</tr>
</tbody>
</table>

**DOR by response**

- Median DOR (95% CI)
  - All responders (n = 95): 21.8 (21.8-NE)
  - sCR (n = 76): NE (21.8-NE)
  - VGPR or better (n = 92): 21.8 (21.8-NE)

DOR, duration of response; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

*CR plus VGPR plus PR.

**Boxed Warning**

- **Cytokine release syndrome (CRS):** Severe or life-threatening CRS should be treated with tocilizumab (Actemra) or tocilizumab and corticosteroids. Do not administer cilta-cel to patients with active infection or inflammatory disorders.
- **Immune effector cell-associated neurotoxicity syndrome:** This may occur before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with cilta-cel.
- **Parkinson disease and Guillain-Barré syndrome and their associated complications**
- **Hemophagocytic lymphohistiocytosis/macrophage activation syndrome:** This may occur with CRS or neurologic toxicities.
- **Prolonged and/or recurrent cytopneas with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery**

**Warnings and Precautions**

- Prolonged and recurrent cytopneas
- Infections
- Hypogammaglobulinemia
- Hypersensitivity reactions
- Secondary malignancies
- Effects on ability to drive and use machines

**Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
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**Prior lines of therapy**

- 4
- 3
- ≥ 5

**Refractory disease**

- 42.3%
- 87.6%

**Prior Transplant**

- 90% autologous stem cell transplantation
- 8% of patients received an allogeneic transplant

**High-risk cytogenetic profile**

- deletion 17p
- translocation (14;16)
- translocation (4;14)

**References**

DURABLE STRENGTH

THE NINLARO® (ixazomib) REGIMEN* OFFERS EXTENDED EFFICACY AND MANAGEABLE TOLERABILITY†,†

The NINLARO regimen extended median PFS by ~6 months vs the Rd regimen.* Median PFS: 20.6 vs 14.7 months for the NINLARO and Rd regimens, respectively; HR=0.74 (95% CI, 0.59-0.94); p=0.012.†,†

Continuous treatment with a proteasome inhibitor (PI)-based regimen is associated with clinical benefits in multiple myeloma.†,†,†,†

*The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The Rd regimen included placebo+lenalidomide+dexamethasone.

†TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral PI) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.†

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Thrombocytopenia has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.

- Gastrointestinal Toxicities, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

Please see additional Important Safety Information on the next page and accompanying Brief Summary.
**WARNINGS AND PRECAUTIONS**

- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

- **Cutaneous Reactions**: Rash, most commonly maculopapular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.

- **Thrombotic Microangiopathy**: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reintroducing NINLARO therapy in patients previously experiencing TTP/HUS is not known.

- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.

- **Embryo-fetal Toxicity**: Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. NINLARO can cause fetal harm.

**ADVERSE REACTIONS**
The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

**DRUG INTERACTIONS**: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

**SPECIAL POPULATIONS**

- **Hepatic Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
- **Lactation**: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.


Please see accompanying Brief Summary on the following pages.
5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animal studies. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose.

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360).

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>69 (19)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periphera neuropathies*</td>
<td>100 (28)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (42)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>122 (34)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>92 (26)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>79 (22)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>68 (19)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>74 (21)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>91 (25)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.
*Represents a pooling of preferred terms

Table 5 represents pooled information from adverse event and laboratory data.

Table 5: Thrombocytopenia and Neutropenia

<table>
<thead>
<tr>
<th></th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>281 (78)</td>
<td>93 (26)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>240 (67)</td>
<td>93 (26)</td>
</tr>
</tbody>
</table>

Herpes Zoster
Herpes zoster was reported in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider’s discretion. Patients treated in the NINLARO regimen who

(Continued on next page)
received antiviral prophylaxis had a lower incidence (< 1%) of herpes zoster infection compared to patients who did not receive prophylaxis (6%).

Eye Disorders
Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO regimen and 1% in the placebo regimen.

Adverse Reactions Reported Outside of the Randomized Controlled Trial
The following serious adverse reactions have each been reported at a frequency of < 1%: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS
7.1 Strong CYP3A Inducers: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John’s Wort).

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy:
Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ixazomib caused embryo-fetal toxicity in pregnant rabbits and rats at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively, Animal Data. In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities (caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses that were also maternally toxic (≥ 0.3 mg/kg). Exposures in the rabbit at 0.3 mg/kg were 1.9 times the clinical time averaged exposures at the recommended dose of 4 mg. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend towards decreased fetal viability, and increased post-implantation losses at 0.16 mg/kg. Exposures in rats at the dose of 0.6 mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

8.2 Lactation: Risk Summary: There are no data on the presence of ixazomib or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions from NINLARO in a breastfed infant, advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential: NINLARO can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO. Contraception: Females: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the final dose. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days after the final dose.

8.4 Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment: In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: Overdosage, including fatal overdosage, has been reported in patients taking NINLARO. Manifestations of overdosage include adverse reactions reported at the recommended dosage. Serious adverse reactions reported with overdosage include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death. In the event of an overdose, monitor for adverse reactions and provide appropriate supportive care. NINLARO is not dialyzable.

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-approved patient labeling (Patient Information). Dosing Instructions
• Instruct patients to take NINLARO exactly as prescribed.
• Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdosage has led to death.
• Advise patients to take NINLARO at least one hour before or at least two hours after food.
• Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
• Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
• Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
• If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥ 72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
• If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
• Advise patients to store capsules in their original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising [see Warnings and Precautions (5.1)].

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their healthcare providers if these adverse reactions persist [see Warnings and Precautions (5.2)].

Peripheral Neuropathy: Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs [see Warnings and Precautions (5.3)].

Peripheral Edema: Advise patients to contact their healthcare providers if they experience unusual swelling of their extremities or weight gain due to swelling [see Warnings and Precautions (5.4)].

Cutaneous Reactions: Advise patients to contact their healthcare providers if they experience new or worsening rash [see Warnings and Precautions (5.5)].

Thrombotic Microangiopathy: Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur [see Warnings and Precautions (5.6)].

Hepatotoxicity: Advise patients to contact their healthcare providers if they experience jaundice or right upper quadrant abdominal pain [see Warnings and Precautions (5.7)].

Other Adverse Reactions: Advise patients to contact their healthcare providers if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura [see Adverse Reactions (6.1)].

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to terminate their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. Advise women using hormonal contraceptives to also use a barrier method of contraception [see Use in Specific Populations (8.1)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose [see Use in Specific Populations (8.1)].

Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the final dose [see Use in Specific Populations (8.2)].

Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLAROhcp.com.

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Fixed-Duration Therapy Struggles to Find Footing Across Tumor Types

by MEIR RINDE

INVESTIGATORS HAVE EXPLORED FIXED-DURATION systemic therapies as a way to provide patients the opportunity to alleviate toxicities, financial burden, and adherence issues often associated with continuous therapies without the risk of losing efficacy. These treatment options have gained some traction in hematologic malignancies, where advances in drug development and sequencing strategies have afforded investigators the opportunity to conduct trials.

In relapsed chronic lymphocytic leukemia (CLL), for example, a high proportion of patients who receive venetoclax (Venclexta) and rituximab (Rituxan) achieve durable remissions, and those with deep responses have the same progression-free survival (PFS) rates whether they received continuous therapy or a fixed 2-year regimen.1 In advanced melanoma, data show little benefit in remaining on checkpoint inhibitors for longer than 2 years, and in some patients just 1 year of therapy provides lasting PFS benefit.2

With other cancers, however, the search for treatments that can be stopped or paused after a relatively short period of time has been stymied by a lack of therapies that induce deep responses in significant numbers of patients. Additionaly, few studies compare limited-duration and continuous therapies and investigators face challenges in terms of accruing patients in clinical trials.

In non-small cell lung cancer (NSCLC), a significant fraction of patients can safely pause their immunotherapy but creating a trial to determine the optimal duration would be difficult, said Chul Kim, MD, an assistant professor at Georgetown University and a physician at Georgetown Lombardi Comprehensive Cancer Center and MedStar Georgetown University Hospital in Washington, DC. “There are patients who achieve good disease response and stabilization on immunotherapy for 2 years, but lung cancer in general is more aggressive. Response to immunotherapy and overall survival [OS] is much better in melanoma, for example,” Kim said. “We don’t see complete responses that often in lung cancer. It would be a great study to conduct, but that would require a pretty big effort. At individual centers there will not be a lot of people you can find to randomize to a study.”

Meanwhile, in some diseases such as multiple myeloma, the introduction of new agents shifted paradigms in the other direction, away from fixed-duration therapies and toward maintenance therapies that may be costly but provide better outcomes in the long term.

FIXED AND CONTINUOUS OPTIONS IN HEMATOLOGIC MALIGNANCIES

Until a decade ago the typical treatment regimen for patients with CLL was a fixed course of chemoimmunotherapy that was repeated upon relapse and tended to become less effective over time, said Shuo Ma, MD, PhD, an associate professor of medicine at Northwestern University Feinberg School of Medicine and a physician at Robert H. Lurie Comprehensive Cancer Center of Northwestern University, in Chicago, Illinois. Standard treatments have shifted in the frontline setting and for patients with relapsed CLL, ushering in an era of continuous therapy with ibrutinib (Imbruvica) or another Bruton tyrosine kinase (BTK) inhibitor, and fixed-duration venetoclax with a monoclonal antibody, she said.

Ma coauthored a study in 2017 on the efficacy of venetoclax plus rituximab (VenR) in relapsed CLL, and results from a 5-year follow-up study were published in 2021. Patients in the phase 1b trial (NCT01682616) received daily oral venetoclax and a monthly injection of rituximab for 6 months followed by venetoclax monotherapy. Discontinuation of therapy was allowed for those who achieved a complete response (CR), CR with incomplete marrow recovery (CRI), or who had undetectable minimal residual disease (uMRD), defined as less than 10^-4 by flow cytometry. At the time of disease progression, patients could be retreated with VenR.3
Fixed-Duration Therapy

The evaluable population included 49 patients; the 5-year overall response rate was 86% (95% CI, 73%-94%), with 53% (95% CI, 38%-68%) achieving CR/CRI. Among responders, 29% achieved CR/CRI within in 1 year, 16% between 1 and 2 years, and 8% after 2 years. The median overall survival (OS) was not reached, and the 5-year OS rate was 86% (95% CI, 72%-94%). In terms of PFS the median was 5.6 years (95% CI, 3.1-6.6) and the 5-year rate was 56% (95% CI, 40%-70%). The median duration of response was 6.2 years (95% CI, 3.9-6.3) with a 5-year ongoing response rate of 58% (95% CI, 40%-73%).

Thirty-three patients achieved a deep response, defined by investigators as CR and/or uMRD. Among these responders, 14 opted for continuous venetoclax monotherapy for a median of 5.6 years (range, 2.4-6.6) and 19 chose limited-duratiion therapy with venetoclax, which received for a median of 1.4 years (range, 0.4-4.2).

Among the responders who received continuous venetoclax, 8 remained in ongoing remission and the 5-year PFS rate was 78% (95% CI, 47%-93%) with a median PFS of 6.6 years (95% CI, 4.4-6.6). The rates were similar for those who stopped treatment with venetoclax, with a median PFS of 6.5 years (95% CI, 3.6-6.5) and a 5-year PFS rate of 80.0% (95% CI, 49.4%-93.0%). The 5-year estimates for ongoing remission were 71% (95% CI, 39%-88%) for those receiving continuous therapy vs 78% (95% CI, 49%-93%) for those receiving limited-duration therapy.

Ma noted that despite providing the opportunity to stop or pause therapy, fixed-duration VenH has not displaced continuous BTK inhibition in CLL, in part because patients do not find oral medications burdensome. “Most [patients] are tolerating [the drug] very well. They’re used to taking a chronic medication every day, just like they’re taking their blood pressure or cholesterol medication every day. For most patients it’s actually not a big problem, especially if they don’t have the high co-pay,” she said.

In addition, the venetoclax combination is not a cure. “Both classes of treatment are very widely used, and most likely a patient with CLL will be using both of those classes in their treatment history—one class is not going to be able to control the disease forever, so you have to go to the next one. It’s just a matter of sequence,” Ma said.

CLL trials continue to investigate optimal treatment duration, often in the context of combinations or sequences that might increase the frequency of deep responses, she continued. Investigators are also using markers, such as uMRD to trace the efficacy of regimens among responders. For example, in the phase 2 CAPTIVATE study (NCT02910583), venetoclax plus ibrutinib was evaluated in patients with treatment-naive CLL. After initial therapy, those with confirmed uMRD are randomly assigned to double-blind placebo or ibrutinib, and those without uMRD are assigned to open-label ibrutinib or ibrutinib plus venetoclax.

In the primary analysis, patients with confirmed uMRD who were randomly assigned to placebo or continued ibrutinib had similar 1-year disease-free survival (DFS) at 95% and 100%, respectively. In an updated analysis presented at the 63rd American Society of Hematology Annual Meeting and Exposition, no new MRD relapses, instances of progressive disease, or deaths were reported among the 43 patients in either arm with confirmed uMRD. In this patient population the 2-year DFS rate in the MRD-guided placebo arm remained at 95.3% (95% CI, 82.7%-98.8%) and the 2-year DFS rate for patients who received ibrutinib remained at 100%; 3-year estimated PFS rates were 95% and 100%, respectively.

CUTOFFS FOR IMMUNOTHERAPY IN MELANOMA

Two years of immunotherapy is probably sufficient for most patients with melanoma, according to Geoffrey T. Gibney, MD, coleader of the Melanoma Disease Group at Georgetown Lombardi Comprehensive Cancer Center and MedStar Cancer Network. However, as is the case other solid tumors, the optimal duration remains a matter of debate given a lack of trials that stop treatment at a predetermined time or directly compare fixed and continuous regimens.

“We recognize, as a melanoma community, that we need more answers. How much treatment does a patient actually need?” Gibney said.

The 2-year consensus is based on results of studies which show durable responses in subsets of patients who reach that benchmark. Gibney cited KEYNOTE-006 (NCT01866319), in which 556 patients received pembrolizumab (Keytruda) and of whom 103 (19%) completed 2 years of the..
Fixed-Duration Therapy

drug. Within that subgroup, 21 (20%) achieved a best overall response of CR, 69 (67%) achieved PR, and 13 (13%) had stable disease (SD).

Results of a 5-year follow-up analysis demonstrated ongoing responses in 76% of the patients who had completed 2 years of pembrolizumab and achieved CR. Ongoing responses were shown among 77% of patients with PR, and 54% of those with SD. Additionally, 23 patients who stopped pembrolizumab early, as allowed by the protocol, and who did not complete 2 years of the drug had a 24-month PFS rate of 86.4% (95% CI, 63.4%-95.4%), which is similar to that in patients with CR who did complete 2 years.

Other relevant trials include KEYNOTE-001 (NCT01295827). In a 5-year follow-up analysis, most patients (90%) who met the criteria for stopping pembrolizumab and entered observation maintained their responses. Of 655 enrolled participants, 72 met the criteria and entered observation. This population included 67 patients with a CR and 5 with a PR.

In a pooled analysis of CheckMate 067 (NCT01844505) and CheckMate 069 (NCT01927419), 56 of 96 patients who discontinued nivolumab (Opdivo) plus ipilimumab (Yervoy) in the first 12 weeks because of toxicity achieved an objective response. Further, investigators observed ongoing responses in 64% of the responding patients. To better identify patients who may safely discontinue immunotherapy, Gibney and his colleagues at Georgetown Lombardi Comprehensive Cancer Center conducted a study using PET/CT scans to assess for active disease. Investigators at the institution offered patients with advanced melanoma scans after approximately 12 months of therapy to determine whether tumor sites were metabolically active; if they were, the investigators used biopsies to evaluate active residual disease. The results of patients who had disease control and discontinued treatment as a result of toxicity were compared with those who stopped treatment after 12 months using a CT scan to identify CR. Among 122 patients included in the retrospective study, 24 had no active disease and discontinued treatment by choice whereas 28 discontinued because of toxicity. The median treatment durations were 12 months and 4 months, respectively. The 3-year event-free survival (EFS) rates among the 2 groups were 95% and 71%, respectively. The low rates of relapse among patients with no active disease via scan or biopsy led investigators to conclude that discontinuation of anti–PD-1 therapy at 12 months may be a viable option for these patients.

Gibney is now leading PET-Stop (EA6192, NCT04462406), a phase 2 trial by the ECOG-ACRIN Cancer Research Group, to validate these results. Following 1 year of standard-of-care anti–PD-1 therapy, investigators will use fluorodeoxyglucose (FDG)-PET/CT scan and tumor biopsy to guide immunotherapy discontinuation decisions in patients with unresectable stage IIIb/IV melanoma. Gibney said using scans helps overcome patient reluctance to stop treatment early.

“[Conducting] a standard trial, where you have a short duration compared with a long duration [of therapy], may not be very appealing to investigators at various centers or patients,” Gibney said. “Patients are probably going to find more appealing an approach that uses a biomarker-type driven [data], or some other signal that allows them to feel comfortable [so that] when they discontinue their therapy, their disease will hopefully remain in remission.”

Other trials that may illuminate the duration question in melanoma include DANTE (ISRCTN15837212), a randomized phase 3 trial in the United Kingdom evaluating the feasibility of stopping first-line anti–PD-1 monotherapy (nivolumab or pembrolizumab) at 12 months in patients who are progression free. Meantime, investigators of Safe Stop (NL7293), a single-arm prospective trial in the Netherlands, are evaluating early discontinuation of first-line anti–PD-1 therapy for patients with advanced or metastatic melanoma who have a confirmed CR or ongoing PR.

In Canada, the phase 3 STOP-GAP trial (NCT02821013) is randomly assigning patients with unresectable stage III/IV melanoma to 2 years of standard therapy in the absence of disease progression, or treatment until maximal tumor response as determined by at least 2 radiologic measurements, with retreatment at time of progression.

MOVING AWAY FROM FIXED-DURATION THERAPIES

Until about a decade ago, fixed-duration therapies were the norm in multiple myeloma treatment. Patients would receive 4 cycles of an initial therapy followed by transplant, or 1 to 2 years of therapy if they were ineligible for transplant, followed by observation, said S. Vincent Rajkumar, MD, a professor of medicine and consultant in the Division of Hematology, Department of Internal Medicine and in the

FIGURE 1. Monitoring for Active Disease in Melanoma: PET-Stop Study Design

ClinicalTrials.gov identifier: NCT04462406

patients with advanced melanoma with disease control and PET/CT scan performed 52 weeks following start of anti–PD-1 therapy

PET/CT scan negative for active disease

Discontinue therapy and monitor with CT scan for disease progression every 12 weeks

Positive for viable tumor or unable to obtain sample

Continue therapy and perform CT scan every 12 weeks

Biopsy

Negate for viable tumor

Discontinue therapy and monitor with CT scan for disease progression every 12 weeks

PET/CT scan positive for active disease

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Fixed-Duration Therapy

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Some trials have shown intriguing examples of durable responses. For example, a 5-year follow-up analysis of the phase 1 CA209-003 trial (NCT00730639) demonstrated that patients with NSCLC treated with 2 years of nivolumab may achieve long-term survival benefit. Among 129 patients with pretreated, advanced NSCLC the 5-year OS rate was 16%, which aligns with data from the 3-year follow-up that showed an OS rate of 18%. The median OS was consistent at 9.9 months (95% CI, 7.8-12.4). Investigators noted that the findings are encouraging, but that an optimal treatment duration has yet to be determined.

Results of other studies have not supported fixed-duration treatments. In an exploratory analysis, the phase 3 CheckMate153 trial (NCT02066636) patients with pretreated, advanced NSCLC were randomly assigned to receive continuous nivolumab (n = 127) or 1-year fixed duration treatment (n = 125). Of the randomized population, the PFS populations included 89 and 85 patients, respectively. At 13.5 months’ follow-up the median PFS was 24.7 months (95% CI, 14.8-18.7) in the continuous therapy arm vs 9.4 months (95% CI, 5.6-13.0) in the fixed-duration arm (HR, 0.56; 95% CI, 0.37-0.84). At 1 and 2 years the PFS rates were 64% and 51% for continuous nivolumab vs 44% and 30.7% for fixed-duration therapy. For those who had SD, investigators noted that continuous and fixed-duration therapy had similar outcomes with a median PFS of 11.8 months (95% CI, 7.0-21.8) vs 9.4 months (95% CI, 9.4-20.7), respectively (HR, 1.01; 95% CI, 0.51–2.11). Some critiques of the trial were that the analysis included only a small fraction of the initial CheckMate153 population and randomly assigned only nonprogressing patients and that the trial design did not mandate SD and durable disease response for this analysis. Additionally, outside of CheckMate153, several unanswered questions remain concerning retrospective-type studies, such as examinations of overtreatment with immune-checkpoint inhibitors and the presence of biomarkers that offer prognostic significance.

Kim said he was not aware of any current trials looking at optimal duration of immunotherapy in NSCLC, as investigators tend to focus on novel agents or combinations, such as 4-drug regimens in first-line disease or a second immunotherapy added to pembrolizumab. For his patients who are receiving immunotherapy, his approach depends in part on what they are comfortable doing.

“After 2 years, if there’s good response, then I have a discussion with the patient. If they want to stop, we hold and watch it, and hopefully nothing happens. If something happens and there’s progression, then we put the patient back on the pembrolizumab,” he said. “But there are some patients who just don’t want to stop, especially when they feel great. They are a little concerned about the uncertainty about what would happen if the treatment were stopped. Some people don’t want to rock the boat.”

REFERENCES
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Frontline Maintenance Avelumab Shows Consistent OS Benefit in Advanced Urothelial Cancer

by GINA MAURO

AVELUMAB (BAVENCIO) PLUS BEST supportive care (BSC) as a frontline maintenance option for patients with metastatic urothelial cancer continued to show an improvement in overall survival (OS) compared with BSC alone, according to updated findings from an exploratory analysis of the phase 3 JAVELIN Bladder 100 trial (NCT02603432).1

With an additional 19 months of follow-up, the median OS with avelumab plus BSC was 23.8 months (95% CI, 19.9-28.8) compared with 15.0 months (95% CI, 13.5-18.2) with BSC alone (HR, 0.76; 95% CI, 0.631-0.915; P = .0036). The 2- and 3-year OS rates with avelumab/BSC (n = 350) were 49.8% and 36.0%, respectively. These rates were 38.4% and 29.8%, respectively, in the BSC-alone arm (n = 350).

Additional data presented during the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium showed the investigator-assessed progression-free survival (PFS) was 3.5 months (95% CI, 4.2-7.2) with avelumab/BSC vs 2.1 months (95% CI, 1.9-3.0) with BSC alone, translating to a 46% reduction in the risk of disease progression or death (HR, 0.54; 95% CI, 0.457-0.645; P < .0001). The 2- and 3-year PFS rates were 23.4% and 15.9%, respectively, with avelumab/BSC, and 7.1% and 5.3%, respectively, with BSC alone (TABLE).1

Lead study author Thomas Powles, MBBS, MRCGP, MD, reviewed the updated findings in a poster presentation. “These data show this consistent survival signal, a HR of 0.76 remains clinically meaningful, and this remains the standard of care for those patients with metastatic urothelial cancer who receive first-line chemotherapy. Sequencing maintenance avelumab remains attractive for these patients, across broad subgroups of patients, with no new safety signals,” said Powles, who is a professor of genitourinary oncology, lead for solid tumor research, and director of Barts Cancer Centre at St Bartholomew’s Hospital in London, England.

In the phase 3 JAVELIN Bladder 100 trial, 700 patients with unresectable locally advanced or metastatic urothelial cancer were randomized 1:1 to receive avelumab plus BSC or BSC alone until disease progression, unacceptable toxicity, or withdrawal. A total of 358 patients had PD-L1-positive disease.

To be eligible for participation, patients must have had a complete response (CR), partial response (PR), or stable disease (SD) with standard frontline chemotherapy with either cisplatin/gemcitabine or carboplatin/gemcitabine for 4 to 6 cycles. Stratification factors included best response to frontline chemotherapy (CR or PR vs SD) and metastatic site (visceral vs nonvisceral) when initiating frontline chemotherapy.

The primary end point of the trial was OS in all randomized patients and in the PD-L1-positive population. Secondary end points included PFS, objective response per RECIST 1.1 criteria, and safety.

In June 2020, data from JAVELIN Bladder 100 led to the FDA approval of frontline maintenance avelumab plus BSC for patients with advanced urothelial cancer who did not progress on frontline platinum-based chemotherapy. At the data cutoff of the earlier analysis, the median OS was 21.4 months (95% CI, 18.9-26.1) with the addition of avelumab compared with 14.3 months (95% CI, 12.9-17.9) with BSC alone (HR, 0.69; 95% CI; 0.56-0.86; 1-sided P = .0005).2 The updated analysis included at least 2 years of follow-up in all patients, bringing it to a median follow-up of 38 months. The data cutoff date was June 4, 2021.2

Investigators reported an OS benefit was observed across most prespecified subgroups and was found irrespective of site of metastases (visceral: HR, 0.91; 95% CI, 0.713-1.163; nonvisceral: HR, 0.60; 95% CI, 0.451-0.798) and type of chemotherapy used (gemcitabine/cisplatin: HR, 0.78; 95% CI, 0.607-1.008; gemcitabine/carboplatin: HR, 0.70; 95% CI, 0.523-0.929; gemcitabine/carboplatin/cisplatin: HR, 0.69; 95% CI, 0.294-1.639). The benefit was not seen in those from Australia (HR, 1.29; 95% CI, 0.697-2.398) and those with liver lesions at baseline (HR, 0.95; 95% CI, 0.585-1.541).
“The forest plot analysis shows avelumab is outperforming BSC across broad subgroups of patients, irrespective of the sites of metastasis, and the type of chemotherapy used, at the PD-L1 status,” Powles said. “This is an important finding and consistent with what was previously shown.”

Among all treated patients (n = 700), 52.9% of patients in the avelumab/BSC arm discontinued and received subsequent therapy with a PD-1/PD-L1 inhibitor (11.4%), FGFR inhibitor (2.9%), or another drug (50.6%). In the BSC-alone arm, 72.0% of patients discontinued treatment and went onto a PD-1/PD-L1 inhibitor (53.1%), FGFR inhibitor (3.7%), or another drug (44.6%). “Subsequent therapy is really important in this setting,” Powles said. “Here, 72% of patients who were randomized to BSC received subsequent therapy. In urothelial cancer, it’s often not easy to give [patients] subsequent therapy. So this is a high percentage.”

In the investigative and control arms, 12.3% and 2.9% of patients, respectively, were still receiving study treatment. Of the subgroups who received subsequent therapy (n = 437), 21.6% of those on the avelumab arm (n = 185) were treated with a PD-1/PD-L1 inhibitor, 5.4% a FGFR inhibitor, and 95.7% another drug. These rates were 73.8%, 5.2%, and 61.9%, respectively, in the BSC-alone arm (n = 252).

For patients who discontinued study treatment because of progressive disease (n = 484), 75.6% of those on avelumab/BSC (n = 209) discontinued and received subsequent treatment with a PD-1/PD-L1 inhibitor (12.9%), FGFR inhibitor (4.8%), or another drug (72.2%). Of those in this subgroup who had received BSC alone (n = 275), 81.8% of patients discontinued and received subsequent therapy with a PD-1/PD-L1 inhibitor (60.4%), FGFR inhibitor (4.0%), or another drug (35.6%).

Regarding safety, Powles noted the long-term safety profile with avelumab, which was analyzed in patients receiving the combination for at least 12 months, was consistent with prior studies of the single-agent checkpoint inhibitor. All-grade and grade 3 or higher treatment-emergent adverse effects (TEAEs) that occurred after at least 12 months of treatment were reported in 86.4% of patients who received avelumab/BSC (n = 118) and 47.5% were grade 3 or higher. These effects occurred with onset at any time (n = 344) in 98.3% of patients, and 53.8% of patients had grade 3 or higher TEAEs with onset at any time.

Additionally, any-grade and grade 3 or higher treatment-related adverse events (TRAEs) occurring after at least 12 months of treatment occurred in 50.0% and 11.9% of patients. These rates were 78.2% and 19.5%, respectively, at any time.

Furthermore, at onset after at least 12 months of treatment, serious TEAEs occurred in 23.7% of patients and serious TRAEs were reported in 5.1% of patients; 36.4% experienced TEAEs that led to interruption of avelumab and 11.0% had TEAEs that led to discontinuation. TEAEs and TRAEs that led to death occurred in 2.5% and 0.8% of patients, respectively. All-grade infusion-related reactions were reported in 3.4% of patients.

For onset of adverse events that occurred at any time, serious TEAEs occurred in 30.5% and serious TRAEs were reported in 10.2% of patients; 45.3% of patients had TEAEs that led to avelumab interruption and 14.2% had TEAEs that led to discontinuation. TEAEs and TRAEs that led to death occurred in 2.0% and 0.6% of patients, respectively. All-grade infusion-related reactions were reported in 21.8% of patients. Of note, 1 patient experienced immune-mediated nephritis after at least 1 year of the combination that led to death.

REFERENCES
ZFJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status.1-4

**Indication**

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

**Important Safety Information**

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

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

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

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

**Embryo-fetal toxicity and lactation:** Based on its mechanism of action, ZFJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZFJULA. Because of the potential for serious adverse reactions from ZFJULA in breastfed infants, advise lactating women not to breastfeed during treatment with ZFJULA and for 1 month after receiving the final dose.

**Zejula Referendum:**

In patients who were administered a starting dose of ZFJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients.

**Primary Endpoint Measurement:**

PR = partial response. HRd = homologous recombination deficient; PFS = progression-free survival; CI = confidence interval; CR = complete response; HR = hazard ratio; 1L = first-line
YOU RESPOND WITH ZEJULA®

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS1,2

OVERALL POPULATION
(N=733)

HRd POPULATION
(n=373)

38%

57%

Reduction in the risk of progression or death

Reduction in the risk of progression or death

MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO
(HR, 0.62; 95% CI, 0.50-0.76) P<0.0001

MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO
(HR, 0.43; 95% CI, 0.31-0.59) P<0.0001

Study Design1,2: PRIMA, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to first-line platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

Important Safety Information (continued)

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

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

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

Please see Brief Summary on the following pages.


1L = first-line; CI = confidence interval; CR = complete response; HR = hazard ratio; HRd = homologous recombination deficient; PFS = progression-free survival; PR = partial response.

Visit ZEJULAHCP.COM to explore the PRIMA data

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1 INDICATIONS AND USAGE

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

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

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies
ZELJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
- a deleterious or suspected deleterious BRCA mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia
Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received monotherapy with ZELJULA in clinical trials. In 1,785 patients treated with ZELJULA in clinical trials, MDS/AML was observed in 15 patients (0.8%).

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

5.2 Bone Marrow Suppression
Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or pan cytopenia have been reported in patients treated with ZELJULA (see Adverse Reactions (6)).

In PRIMA, the overall incidences of ≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZELJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZELJULA based on baseline weight or platelet count,

≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 23%, and 15%, respectively, of patients receiving ZELJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

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

In QUADRA, ≥Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 28%, 27%, and 13%, respectively, of patients receiving ZELJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients.

Do not start ZELJULA until patients have recovered from hematological toxicity caused by previous chemotherapy (≥Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZELJULA and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) of full prescribing information).

5.3 Hypertension and Cardiovascular Effects
Hypertension and hypertensive crisis have been reported in patients treated with ZELJULA.

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZELJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In QUADRA, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZELJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with ZELJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the dose of ZELJULA, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).

5.4 Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZELJULA in clinical trials and has also been described in postmarketing reports (see Adverse Reactions (6.2)). Signs and symptoms of PRES include seizure, headache, altered mental status, visual disturbance, or corticalblindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging.

Monitor all patients treated with ZELJULA for signs and symptoms of PRES. If PRES is suspected, promptly discontinue ZELJULA and administer appropriate treatment. The safety of reinitiating ZELJULA in patients previously experiencing PRES is not known.

5.5 Embryo-Fetal Toxicity
Based on its mechanism of action, ZELJULA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) of full prescribing information). ZELJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients. ZELJULA is genotoxic and targets actively dividing cells in animals and patients (see Nonclinical Toxicology (13.2) of full prescribing information).

Due to the potential risk to a fetus based on its mechanism of action, animal development, and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZELJULA (see Use in Specific Populations (8.1, 8.3)).

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

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- MDS/AML (see Warnings and Precautions (5.1))
- Bone marrow suppression (see Warnings and Precautions (5.2))
- Hypertension and cardiovascular effects (see Warnings and Precautions (5.3))
- Posterior reversible encephalopathy syndrome (see Warnings and Precautions (5.4))

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

The most common adverse reactions of all grades in >10% of 1,314 patients who received ZELJULA in the placebo-controlled PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), diziness (14%), acute kidney injury (13%), urticarial infection (12%), and hypoglycemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer
The safety of ZELJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZELJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZELJULA in PRIMA
Serious adverse reactions occurred in 32% of patients receiving ZELJULA. Serious adverse reactions in ≥2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZELJULA. Adverse reactions resulting in permanent discontinuation in ≥3% of patients who received ZELJULA included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2%) each. Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (53%), and neutropenia (20%).

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

(continued on next page)
1. Maintenance Treatment of Recurrent Ovarian Cancer

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

2. Maintenance Treatment of Recurrent Ovarian Cancer

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%), anemia (20%), and neutropenia (15%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

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

Table 4: Adverse Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA

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

Table 7: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in NOVA

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA

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

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in QUODRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUODRA population, the median duration was 4 months (range: 0.10 to 32 months). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in ≥5% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUODRA.
6.2 Postmarketing Experience

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

Blood and lymphoid system disorders

Neutropenia includes events with preferred terms of neutropenia, AST/ALT = aspartate transaminase/alanine aminotransferase.

Immune System Disorders: Hypersensitivity (including anaphylaxis).

Neurological System Disorders: Posterior reversible encephalopathy syndrome (PRES).

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

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

Skin and Subcutaneous Tissue Disorders: Phototoxicity.

Vascular Disorders: Hypertensive crisis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Hypertension

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

Contraception

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In PRIMA, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. In NOVA, 35% of patients were aged 65 years or older and 8% were aged 75 years or older. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily (see Dosage and Administration (2.4) of full prescribing information). Niraparib exposure increased in patients with moderate hepatic impairment (total bilirubin ≥1.5 x upper level of normal [ULN] to 3.0 x ULN and any aspartate transaminase [AST] level >3 x ULN and any AST level >3 x ULN and AST > ULN) no dose adjustment is needed.

The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST level) (see Clinical Pharmacology (12.3) of full prescribing information).

17 PATIENT COUNSELING INFORMATION

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

Myelodysplastic Syndromes/Acute Myeloid Leukemia

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts or a need for blood transfusions. This may be a sign of hematological toxicity or MDS or AML, which may have been reported in patients treated with ZEJULA (see Warnings and Precautions (5.1)).

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection (see Warnings and Precautions (5.2)).

Hyper tension and Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first 2 months, then monthly for the first-year of treatment and periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated (see Warnings and Precautions (5.3)).

Posterior Reversible Encephalopathy Syndrome

Inform patients that they are at risk of developing posterior reversible encephalopathy syndrome (PRES) that can present with signs and symptoms including seizure, headaches, altered mental status, or vision changes. Advise patients to contact their healthcare provider if they develop any of these signs or symptoms (see Warnings and Precautions (5.4)).

Dosing Instructions

Inform patients on how to take ZEJULA (see Dosage and Administration (2.2) of full prescribing information). ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy (see Warnings and Precautions (5.5) and Use in Specific Populations (8.11)).

Contraception

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

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose (see Use in Specific Populations (8.2)).

Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

Advise patients that ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have aspirin hypersensitivity (see Warnings and Precautions (5.6)).

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Frontline Niraparib Plus Abiraterone Improves rPFS in HRR Gene–Altered mCRPC

by CAROLINE SEYMOUR

DATA FROM PROSPECTIVELY SELECTED biomarker cohorts in the phase 3 MAGNITUDE trial (NCT03748641) demonstrated that the combination of niraparib (Zejula) and abiraterone acetate (Zytiga) and prednisone led to a significant improvement in radiographic progression-free survival (rPFS) vs placebo plus abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations.

At a median follow-up of 18.6 months, niraparib plus abiraterone led to a 47% reduction in the risk of progression or death in patients with BRCA1/2 mutations and a 27% reduction in the risk of progression or death in all patients with HRR gene alterations vs placebo plus abiraterone.

In the BRCA1/2 population, the median rPFS was 16.6 months with niraparib plus abiraterone vs 10.9 months with placebo plus abiraterone (HR, 0.53; 95% CI, 0.36-0.79; P = .0014) by central review. The investigator-assessed rPFS was 19.3 months with niraparib/abiraterone and 12.4 months with placebo/abiraterone (HR, 0.50; 95% CI, 0.33-0.75; P = .0006).

Among all patients with HRR gene alterations, the median rPFS by central review was 16.5 months vs 13.7 months, respectively (HR, 0.73; 95% CI, 0.56-0.96; P = .0217). Here, the investigator-assessed rPFS was 19.0 months and 13.9 months, respectively (HR, 0.64; 95% CI, 0.49-0.86; nominal P = .0022).

"The MAGNITUDE study results support niraparib plus abiraterone as a new first-line treatment option for patients with mCRPC and alterations in genes associated with HRR," lead study author Kim N. Chi, MD, said in a presentation of the data during the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium. Chi is a professor in the Department of Medicine at the University of British Columbia (BC), a senior research scientist at the Vancouver Prostate Centre, and chief medical officer and vice president of BC Cancer, in Canada.

As many as 30% of patients with mCRPC will harbor alterations in genes associated with HRR. Although these alterations reflect poor prognosis, they have also shown increased sensitivity to PARP inhibitors, such as niraparib, Chi explained. Notably, the addition of an antiandrogen agent, such as abiraterone, has been theorized to augment responses in all-comers and served as the rationale for the randomized, double-blind MAGNITUDE trial, which evaluated the value of adding niraparib to abiraterone in patients with mCRPC with and without HRR gene alterations.

The study enrolled patients with mCRPC who had received no more than 4 months of prior abiraterone and prednisone for mCRPC, had an ECOG performance status of 0 or 1, and had a Brief Pain Inventory-Short Form worst pain score of 3 or less. Eligible patients were screened for HRR alterations in ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, and PALB2.

Based on prescreening results, patients were allocated into the biomarker-positive cohort or the biomarker-negative cohort, which had a planned enrollment of 400 and 600 patients, respectively. Patients were randomized 1:1 to receive 200 mg of niraparib once daily plus abiraterone or placebo plus abiraterone in each of the cohorts.

The primary end point was rPFS assessed by blinded independent central review in the BRCA1/2 population, followed by all other biomarker populations. Secondary end points were the time to initiation of cytotoxic chemotherapy, time to symptomatic progression, and overall survival (OS). Other end points included time to prostate-specific antigen (PSA) progression, objective response rate (ORR), time to second disease progression, time to pain progression, and patient-reported outcomes.

Patients were stratified by prior taxane-based chemotherapy for metastatic castration-sensitive disease, prior androgen receptor inhibitor for nonmetastatic castration-resistant disease or metastatic castration-sensitive disease, prior abiraterone plus prednisone for frontline mCRPC treatment, and BRCA1/2 vs other HRR gene alterations. The statistical analysis included a prespecified futility analysis in the biomarker-negative population after approximately 200 patients were enrolled and approximately 125 composite events of either radiographic or PSA progression or death had occurred.

Findings from the preplanned futility analysis in 233 biomarker-negative patients failed to show the benefit of adding niraparib to abiraterone in the prespecified composite end point of radiographic or PSA progression (HR, 1.09; 95% CI, 0.75-1.59). With added grade 3/4 toxicity in the niraparib arm, the independent data monitoring committee recommended halting enrollment to this cohort. As such, 423 patients with HRR gene alterations were subsequently randomized to niraparib plus abiraterone (n = 212) or placebo plus abiraterone (n = 211).

### TABLE. Outcomes in Biomarker Cohorts of the MAGNITUDE Study

<table>
<thead>
<tr>
<th></th>
<th>BRCA1 / 2-mutated mCRPC (n = 113)</th>
<th>Placebo plus AAP (n = 112)</th>
<th>All HRR gene–altered mCRPC (n = 212)</th>
<th>Placebo plus AAP (n = 211)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td>rPFS by central review, months</td>
<td></td>
<td></td>
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<tr>
<td>rPFS</td>
<td>16.6 (HR, 0.53; 95% CI, 0.36-0.79; P = .0002)</td>
<td>10.9 (HR, 0.73; 95% CI, 0.56-0.96; P = .0014)</td>
<td>16.6 (HR, 0.59; 95% CI, 0.39-0.89; P = .0108)</td>
<td>13.7 (HR, 0.69; 95% CI, 0.47-0.99; P = .0444)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Time to symptomatic progression, months</td>
<td>NE (HR, 0.53; 95% CI, 0.33-1.01; P = .0495)</td>
<td>NE (HR, 0.58; 95% CI, 0.33-1.01; P = .0495)</td>
<td>NE (HR, 0.68; 95% CI, 0.42-1.11; P = .1224)</td>
<td>NE (HR, 0.73; 95% CI, 0.47-1.00; P = .0014)</td>
</tr>
<tr>
<td>Time to PSA progression</td>
<td>NE (HR, 0.46; 95% CI, 0.30-0.69; P = .0002)</td>
<td>9.2 (HR, 0.57; 95% CI, 0.43-0.76; P = .0001)</td>
<td>18.5 (HR, 0.57; 95% CI, 0.43-0.76; P = .0001)</td>
<td>9.3 (HR, 0.57; 95% CI, 0.43-0.76; P = .0001)</td>
</tr>
<tr>
<td>ORR</td>
<td>52% (n = 29/56) (n = 113)</td>
<td>31% (n = 15/48) (n = 112)</td>
<td>60% (n = 55/92) (n = 212)</td>
<td>28% (n = 23/82) (n = 211)</td>
</tr>
<tr>
<td>CR</td>
<td>18% (n = 20/113) (n = 113)</td>
<td>14% (n = 16/112) (n = 112)</td>
<td>22% (n = 20/92) (n = 212)</td>
<td>11% (n = 18/162) (n = 211)</td>
</tr>
<tr>
<td>PR</td>
<td>34% (n = 38/113) (n = 113)</td>
<td>17% (n = 19/112) (n = 112)</td>
<td>38% (n = 35/92) (n = 212)</td>
<td>17% (n = 36/208) (n = 211)</td>
</tr>
</tbody>
</table>

AAP: abiraterone acetate plus prednisone/prednisolone; CR: complete response; HRR: homologous recombinational repair; mCRPC: metastatic castration-resistant prostate cancer; NE: not estimable; ORR: overall response rate; PR, partial response; PSA: prostate-specific antigen; rPFS, radiographic progression-free survival.
At baseline, the median age was 69 years (range, 43-100). In the niraparib and placebo arms, respectively, 23.6% (n = 50) and 22.7% (n = 48) of patients had prior abiraterone/ prednisone, 24.1% (n = 51) and 19.5% (n = 39) had visceral metastases, and 46.3% (n = 98) and 43.6% (n = 92) had BRCA1/2 mutations.

Additional findings showed rPFS favored niraparib across all prespecified biomarker-positive subgroups and in secondary and prespecified end points (TABLE). Notably, the addition of niraparib to abiraterone prolonged time to initiation of cytotoxic chemotherapy (HR, 0.59; 95% CI, 0.39-0.89; P = .0108), time to symptomatic progression (HR, 0.69; 95% CI, 0.47-0.99; P = .0444), and time to PSA progression (HR, 0.57; 95% CI, 0.43-0.76; P = .0001) in all patients with HRR gene alterations. Moreover, the ORR was improved with niraparib vs placebo at 60% (n = 53/92) vs 28% (n = 23/82; relative risk, 2.13; P < .001).

Similarly, niraparib delayed the time to initiation of cytotoxic chemotherapy (HR, 0.58; 95% CI, 0.33-1.01; P = .0495), time to symptomatic progression (HR, 0.68; 95% CI, 0.42-1.11; P = .1224), and time to PSA progression (HR, 0.46; 95% CI, 0.30-0.69; P = .0002) in all patients with BRCA1/2 mutations. Additionally, the ORR was improved with niraparib vs placebo, at 52% (n = 29/56) vs 31% (n = 15/48; relative risk, 1.66; P = .035). Although data from the first interim analysis of OS were immature (HR, 0.94; 95% CI, 0.65-1.36; P = .733), a multivariate analysis accounting for baseline characteristics showed favorable outcomes with niraparib (HR, 0.767; 95% CI, 0.525-1.119; P = .1682).

In terms of safety, no new signals were observed by investigators. All-grade treatment-emergent adverse effects (TEAEs) occurred in 71.8% and 51.4% in the olaparib/abiraterone arm, respectively. The most common grade 3/4 TEAEs in the niraparib arm were anemia (29.7%), hypertension (15.6%), and thrombocytopenia and neutropenia (each, 6.6%) vs hypertension (14.2%), anemia (7.6%), and hematotoxicity (4.7%) in the placebo arm.

Dose reductions occurred in 19.8% of patients on niraparib, with a median relative dose intensity of 99%. The most common AEs leading to dose reduction in the niraparib arm were anemia (13.2%) and thrombocytopenia (2.8%). Additionally, 10.8% and 4.7% of patients discontinued treatment in the niraparib and placebo arms due to AEs, respectively. Deaths due to an AE occurred in 11 (5.2%) of patients on niraparib vs 7 (3.3%) of those on placebo.

Notably, no clinically significant differences in overall quality of life were seen between the study arms, according to results from The Functional Assessment of Cancer Therapy-Prostate questionnaire.

“MAGNITUDE highlights the importance of testing for HRR gene alterations in patients with mCRPC to identify who will optimally benefit from the combination of niraparib plus abiraterone,” Chi said.

References

Olaparib/Abiraterone Combo Significantly Improves Radiographic PFS in mCRPC

by GINA MAURO

OLAPARIB (LYNPARZA) IN COMBINATION with abiraterone acetate (Zytiga) led to a 34% reduction in the risk of radiographic disease progression or death compared with placebo and abiraterone as a first-line treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), according to results of the phase 3 PROpel trial (NCT03732820). In a presentation of the data during the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium, lead study author Fred Saad, MD, FRCS, said PROpel is the first combination approach to deliver consistent clinical benefits for patients in the first-line mCRPC setting, irrespective of homologous recombinational repair (HRR) mutation status. “This benefit led to what I think is the longest rPFS we have seen to date in [mCRPC] beyond 2 years,” Saad said, who is a full professor in the Department of Surgery and Raymond Garneau Chair in Prostate Cancer Research at the University of Montreal. Saad also serves as the head of urology at the University of Montreal Hospital Center and the director of prostate cancer research at the Montreal Cancer Institute in Canada.

Specifically, the data showed patients who received olaparib/abiraterone had a median investigator-assessed radiographic progression-free survival (rPFS) of 24.8 months vs 16.6 months with placebo/abiraterone (HR, 0.66; 95% CI, 0.49-0.74; P < .0001), which was statistically significant and clinically meaningful. The 1- and 2-year rPFS rates were 71.8% and 51.4% in the olaparib/abiraterone arm (n = 399), respectively. These rates were 63.4% and 33.6% with placebo/abiraterone (n = 397), respectively. When evaluated by blinded independent central review, the median rPFS with olaparib/abiraterone was 27.6 months vs 16.4 months with placebo/abiraterone, leading to a 39% reduction in the risk of radiographic disease progression or death (HR, 0.61; 95% CI, 0.49-0.67; P < .0001). The 1- and 2-year rPFS rates with olaparib plus abiraterone were 73.8% and 53.7%, respectively. In the placebo/abiraterone arm, these rates were 60.6% and 34.1%, respectively.

Patients with mCRPC who are treated in the frontline setting have a median survival of approximately 3 years in clinical trial settings, Saad noted, adding that approximately half of patients in real-world practice only receive 1 line of active treatment. Here, the median survival is less than 2 years, underscoring an unmet need to improve outcomes in the up-front setting.

Investigators of PROpel looked to build on previously reported data with olaparib in mCRPC, which have shown encouraging results. For example, results from the phase 3 PROfound trial (NCT02987543) demonstrated significantly
prolonged rPFS and overall survival (OS) in patients with mCRPC, following a next-generation hormonal agent (NHA) with HRR gene alterations. Additionally, findings from a phase 2 trial (NCT01972217) of olaparib and abiraterone showed prolonged investigator-assessed rPFS vs placebo/abiraterone in patients with mCRPC following treatment with docetaxel, regardless of HRR status (HR, 0.65; 95% CI, 0.44-0.97; P = .034). In the international, double-blind, phase 3 PROpel trial, investigators randomized patients with mCRPC in the first-line setting 1:1 to receive olaparib at 300 mg twice daily plus abiraterone at 1000 mg daily or placebo and abiraterone at 1000 mg daily. Patients could have received docetaxel in the metastatic hormone-sensitive prostate cancer (mHSPC) setting, but no prior abiraterone was allowed. Other NHAs were permitted if they were stopped at least 12 months prior to study enrollment. Patients also had ongoing androgen deprivation therapy and an ECOG performance status of 0 or 1.

Stratification factors included site of distant metastases (bone only vs visceral vs other) and prior taxane in the mHSPC setting (yes vs no). The primary end point was investigator-assessed rPFS, with OS as a secondary end point. Additional outcome measures included time to first subsequent therapy or death (TFST), time to second progression or death (PFS2), objective response rate (ORR), HRR mutation prevalence (retrospective testing), health-related quality of life, and safety and tolerability.

Baseline characteristics were well balanced between the 2 arms. The median age was 69.5 years (range, 43-91), and most patients had an ECOG performance status of 0 (70.1%). Of note, symptomatic patients (Brief Pain Inventory-Short Form ≥ 4 and/or opiate use) consisted of 25.8% and 20.2% of olaparib- and placebo-treated patients, respectively; 22.5% of patients had received docetaxel at the mHSPC stage. Saad noted 40.3% of the overall study population had measurable disease via RECIST 1.1 criteria at baseline.

Additionally, patients either had HRR mutations (27.8% with olaparib vs 29.0% with placebo), non-HRR mutations (69.9% vs 68.8%, respectively), or unknown HRR mutation status (2.3% each). The median prostate-specific antigen was 17.90 μg/L (interquartile range [IQR], 6.09-67.00) with olaparib/abiraterone and 16.81 μg/L [IQR, 6.26-53.30] with placebo/abiraterone. Most metastases occurred in the bone at 87.5% and 85.4% of patients, respectively. Additional findings showed the rPFS benefit was observed across all prespecified subgroups (TABLE). OS data, which were at 28.6% maturity, showed the median OS was not reached in either arm but trended toward improved survival with olaparib/abiraterone vs placebo/abiraterone (HR, 0.86; 95% CI, 0.66-1.12; prespecified 2-sided α = .29).

TFST also was favored with the addition of olaparib. The median TFST was 25.0 months in the olaparib/abiraterone arm compared with 19.9 months with placebo/abiraterone (HR, 0.74; 95% CI, 0.61-0.90; P = .004). Furthermore, the median PFS2 was not reached in either arm but supported longer-term benefit with olaparib/abiraterone (HR, 0.69; 95% CI, 0.51-0.94; P = .0184).

When evaluated for response, the ORR with olaparib plus abiraterone was 58.4%, with a 4.3% complete response (CR) rate and a 54.0% partial response (PR) rate. The stable disease (SD) rate was 26.1%, and the progressive disease (PD) rate was 13.7%. In the placebo/abiraterone arm, the ORR was 48.1%, which consisted of a 6.3% CR rate and a 41.9% PR rate. The SD and PD rates were 28.1% and 19.4%, respectively. The odds ratio in ORR between olaparib/abiraterone and placebo/abiraterone was 1.60 (95% CI, 1.02-2.53; P = .0409).

Regarding safety, adverse effects (AEs) occurred in 97.2% and 94.9% of olaparib/abiraterone- and placebo/abiraterone-treated patients, respectively. Grade 3 or higher AEs occurred in 47.2% and 38.4% of patients, respectively. AE-related deaths occurred in 4.0% (n = 16) of those on the olaparib arm compared with 4.3% (n = 17) of patients on the placebo arm. Dose interruptions and reductions occurred in 44.7% and 20.1% of patients who received the addition of olaparib. These rates were 25.3% and 5.6% for those on the placebo arm. Additionally, more patients discontinued olaparib due to an AE (13.8%) compared with 7.8% of patients receiving placebo. A total of 8.5% and 8.8% of patients in each arm, respectively, discontinued abiraterone due to an AE.

There were no cases reported of myelodysplastic syndrome or acute myeloid leukemia, and the incidence of new primary cancers and pneumonitis were balanced between the 2 arms, according to Saad. The AE profiles were consistent with the known toxicity profiles of the individual agents. The most common all-grade and grade 3 or higher AE with olaparib was anemia (46.0% and 15.1%, respectively). In the placebo arm, all-grade anemia was reported among 16.4% of patients and at grade 3 or higher among 3.3% of patients, respectively.

Cardiac failure occurred at similar rates between the 2 arms at 1.5% with olaparib and 1.3% with placebo. Arterial thromboembolic events were also similar at 2.0% and 2.5%, respectively. However, numerically higher venous thromboembolic events were reported for olaparib/abiraterone (7.3%) vs placebo/abiraterone (3.3%), with pulmonary embolism being the most reported venous thromboembolic event (6.5% vs 1.8%, respectively). Pulmonary embolism events were mostly incidental findings via CT scans. Saad said this event did not lead to treatment discontinuation with either olaparib or abiraterone. Quality of life was also found to be comparable between the 2 groups.

TABLE. rPFS Outcomes in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Olaparib/abiraterone vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>HR, 0.51; 95% CI, 0.35-0.75</td>
</tr>
<tr>
<td>≥65 years</td>
<td>HR, 0.78; 95% CI, 0.62-0.98</td>
</tr>
<tr>
<td>Site of distant metastases</td>
<td></td>
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<tr>
<td>Bone only</td>
<td>HR, 0.73; 95% CI, 0.54-0.98</td>
</tr>
<tr>
<td>Visceral</td>
<td>HR, 0.62; 95% CI, 0.39-0.99</td>
</tr>
<tr>
<td>Other</td>
<td>HR, 0.62; 95% CI, 0.44-0.85</td>
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<table>
<thead>
<tr>
<th>Prior docetaxel</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>HR, 0.61; 95% CI, 0.40-0.92</td>
</tr>
<tr>
<td>No</td>
<td>HR, 0.71; 95% CI, 0.56-0.89</td>
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<table>
<thead>
<tr>
<th>HRR mutation status</th>
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<tr>
<td>HRR mutant</td>
<td>HR, 0.50; 95% CI, 0.34-0.73</td>
</tr>
<tr>
<td>Non-HRR mutant</td>
<td>HR, 0.76; 95% CI, 0.60-0.97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HRR, homologous recombinational repair; rPFS, radiographic progression-free survival</th>
</tr>
</thead>
</table>

REFERENCES


MORE ON ASCO GU | Conference Highlights
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma1:

**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 trial1-3

**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, and pulmonary edema.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and anaphylaxis. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

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 appropriate
After a median ~30 months of follow-up, mPFS was not reached with DARZALEX® + Rd vs Rd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.1

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

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRRs=Injection-related reactions; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

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

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

With an ~3 to 5 minute subcutaneous injection, DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.1,3

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

At median ~5 years of follow-up:2,3

- Most frequent TEAEs ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthma, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms.

- Grade 3/4 infections were 41% for DRd vs 29% for Rd.

- Grade 3/4 TEAEs ≤10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%).

These ~5-year analyses were not included in the current Prescribing Information.

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

At median ~5 years of follow-up:2,3

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

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

- Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. 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, and hypotension.

- Pre-medicate patients with histamine-1 receptor antagonist, aceterminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

**MAIA Study (N=832)**

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

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

**Systemic Reactions**

In a pooled safety population of 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. 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, and hypotension.
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.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5.5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia
DARZALEX® and DARZALEX FASPRO® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

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

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

DARZALEX® and DARZALEX FASPRO®: Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX® and DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX FASPRO® and for 3 months after the last dose.

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

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

DARZALEX FASPRO®: ADVERSE REACTIONS
In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia. 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 eligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX FASPRO® [daratumumab and hyaluronidase-fihj] is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are 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 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.

References:
Table 3: Adverse Reactions Reported in ≥10% of Patients and With At Least a 5% Greater Frequency in the DRd Arm in POLLUX (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Rd (N=291)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>26</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Nervous system disorders**

<table>
<thead>
<tr>
<th>Key</th>
<th>D-daratumumab, Rd-lenalidomide-dexamethasone.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection bacterial, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute rhinosinusitis, Mycoplasma pneumonia, pharyngitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis epitheloidis, laryngitis viral, oropharyngeal candidiasis, respiratory mononiliais, viral rhinitis, acute tonsillitis, rhino virus infection</td>
</tr>
<tr>
<td></td>
<td>+ Infusion-related reaction is defined as terms determined by investigators to be related to infusion</td>
</tr>
<tr>
<td></td>
<td>cough, productive cough, allergic cough</td>
</tr>
<tr>
<td></td>
<td>dyspnea, dyspepsia exertional</td>
</tr>
</tbody>
</table>

**Laboratory abnormalities worsening during treatment from baseline listed in Table 4.**

**Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DRd (N=283)</th>
<th>Rd (N=291)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td>52</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>52</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>73</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**Hepes Zoster Virus Reactivation**

Prophylaxis for Hepes 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.

**Infecous**

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: D VD: 21% vs. Ve: 19%; DRd: 28% vs. Rd: 23%; DPa: 28%; Dk: 37%; KD: 29%; Kk: 21%
- where carfilzomib 20/56 mg/m² was administered twice-weekly
- where carfilzomib 20/70 mg/m² was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%, DRd: 32%, Rd: 23%, DVTd: 22%, Vtd: 20%
- Pneumonia was the most common Grade 3 or 4 infection in the relapsed/refractory patient studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fetal infections (Grade 5 were reported as follows:

- Relapsed/refractory patient studies: D VD: 1%; Ve: 2%; DRd: 2%; Rd: 1%; DPa: 2%; Dk: 5%; Kk: 3%; KD: 0%;
- where carfilzomib 20/56 mg/m² was administered twice-weekly
- where carfilzomib 20/70 mg/m² was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%, DVTd: 0%, Vtd: 0%.

Fetal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fetal infections were primarily due to pneumonia and sepsis.

**Hepatitis B Virus (HBV) Reactivation**

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

**Other Clinical Trials Experience**

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

**Nervous System disorders:** Syncope

**Immune system**

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 coincidence of antibody inclusion in neutralizing antibodies may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of data obtained using different assays may not be possible. The percentage of patients who develop antibodies with daratumumab includes the percentage of patients who have antibodies with daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

**Pramartxing 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.

**Immunogenicity**

**Drug Interactions**

**Gastrointestinal disorders:** Pancreatitis

**Infections:** Clostridiomycetaceae, Listeriosis

**Embryo-Fetal Toxicity**

DARZALEX (daratumumab) injection

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

DARZALEX can cause fetal harm when administered to a pregnant woman. A US study of the association of daratumumab products was based on 209 women treated with DARZALEX. Data from CD38 knockout animal models (see Data) show that daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference methods include treating reagent RBCs with diithioldithiolum (DTT) to disrupt daratumumab binding (see References or genotyping). Since the Kell blood group system is also sensitive to DTT treatment, supply negative units after ruling out or identifying all antibodies using DTT-treated RBCs.

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

**Embryo-Fetal Toxicity**

Adverse reproductive outcomes with daratumumab have not been observed in animal studies and the limited amount of human data are not sufficient to draw any conclusions about possible embryotoxicity and teratogenicity of daratumumab.

Data from CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

**Embryonic and Fetal Toxicity**

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, lenalidomide, or thalidomide, refer to the labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

**Contraception**

Advises 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 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 Dk group in CANDOVI, 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**

Advises patient to read the FDA-approved patient labeling (Patient Information). In.addition, patients are advised 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, dyspnea, dyspnea exertional.

**Infusion-Related Reactions**

Advises patients to contact their healthcare provider if they have a fever (see Warnings and Precautions).

**TBF-13000/epdf).**

**TRC**

**Thrombocytopenia**

Advises patients to contact their healthcare provider if they notice signs of bruising or bleeding (see Warnings and Precautions).

Advises 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).

Advises patients that DARZALEX may 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**

Advises patients to inform their 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).
DARZALEX FASPRO® (daratumumab and hyaluronidase-fiij) injection, for subcutaneous use

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 822 patients with multiple myeloma (N=439) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO® in monotherapy as part of a combination therapy, 8% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1.1% with repeat injections. The median time to onset was 3.2 hours (range: 9 minutes to 5.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in <1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions included, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, wheezing, as well as anaphylactic reaction, pulmonary edema, chest pain, pruritus, chills, vomiting, nausea, and hypotension.

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 prior to 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).

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.8%. The most frequent (≥1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5.5 minutes (range: 0 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 IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

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

Neutropenia
Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to 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 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 fetal death when administered to a pregnant woman. DARZALEX FASPRO can cause harm to a developing embryo. Advise female patients of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Advise females of reproductive potential to avoid pregnancy (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 Antibody Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab binds 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).

Notify 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 (2.5) in Full Prescribing Information).

Interference with Determination of Complete Blood Count
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 absolute and 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.

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>Fatigue</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 infection</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Bronchitis</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>Dyspnea</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>12</td>
<td>9</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

- Fatigue includes asthenia, and fatigue.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
- Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
- Bronchitis includes bronchitis, and bronchitis viral.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Cough includes cough, and productive cough.
- 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
- Respiratory tract infestations
- General disorders and administration site conditions: chills, infusion reaction, injection site reaction
- Vascular disorders: hypotension, hypertension

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>5</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
<td>9</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

- Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=45).

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 or other hyaluronidase products may be misleading.
In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies. In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 1% of 786 patients developed treatment-emergent anti-Hu/PD1 antibodies. The anti-Hu/PD1 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-Hu/PD1 antibodies tested positive for neutralizing antibodies.

### Pharmakokinetics

The following adverse reactions have been identified with 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.

### Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

### Drug Interactions

Effects of Daratumumab on Laboratory Tests

DARZALEX FASPRO binds to CD38 on RBCs and interacts with compatibility testing, including antibody screening and cross-matching. Daratumumab interference methods include treating reaction RBCs with diethylenetriamine pentaacetic acid (DTP) to disrupt daratumumab binding (see Reference) or genotyping. Since the Kell blood group system is also sensitive to DTP 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.

### Use in Specific Populations

#### Pregnancy

**Risk Summary**

DARZALEX FASPRO 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 CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO 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 FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information for use during pregnancy.

### Clinical Considerations

**Fetal/Neonatal Adverse Reactions**

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

### Data

**Animal Data**

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human dose, had no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation with 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 immunoglobin 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.

### Dosing in Elderly Patients

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

### Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing (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).

### Pregnancy/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).

### Cardiac Toxicity

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).

### 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).
Darolutamide Plus ADT Boosts OS in Metastatic Castration-Sensitive Prostate Cancer

by AUDREY STERNBERG

THE ADDITION OF DAROLUTAMIDE (Nubeqa) to androgen deprivation therapy (ADT) and docetaxel generated better overall survival (OS) vs placebo with ADT and docetaxel in patients with metastatic castration-sensitive prostate cancer (CSPC), according to results of the ARASENS trial (NCT02799602) that were reported at the 2022 Genitourinary Cancers Symposium.1 The results of the trial were simultaneously published in the New England Journal of Medicine.2

At a median follow-up of 43.7 months for darolutamide and 42.4 months with placebo, the active therapy resulted in a 32.5% reduction in the risk of death (HR, 0.68; 95% CI, 0.57-0.80; P < .001). Specifically, the median OS in the darolutamide arm (n = 651) was not estimable (NE; 95% CI, NE-NE) vs 48.9 months (95% CI, 44.4-NE) with placebo (n = 655). Rates of OS at 48 months were 62.7% and 50.4%, respectively.1,2

“Darolutamide improved OS despite a high rate of subsequent life prolonging systemic therapies in the placebo group,” Matthew R. Smith, MD, PhD, the Claire and John Bertucci Endowed Chair group,” Matthew R. Smith, MD, PhD, the

Darolutamide is a structurally distinct and highly potent androgen receptor (AR) inhibitor that was previously approved to treat patients with castration-resistant prostate cancer (CRPC) in the nonmetastatic setting based on results of the phase 3 ARAMIS trial (NCT02200614).3 Data from the study showed a statistically significant improvement in metastasis-free survival with the agent against matched placebo.

In ARASNS, patients with cytologically confirmed metastatic adenocarcinoma of the prostate were eligible for the trial. All participants needed to be candidates for ADT and docetaxel, have an ECOG performance status of 0 or 1, and have adequate organ function.1,2

Patients were randomized 1:1 to either 600 mg of daily darolutamide or matched placebo plus ADT/docetaxel. Factors for stratification included extent of disease (M1b/c) and alkaline phosphatase (ALP) levels. The primary end point was OS with secondary outcome measures of time to CRPC, time to pain progression, time to first symptomatic skeletal event (SSE), time to initiation of subsequent systemic antineoplastic therapy, and safety.

Patient characteristics were well balanced between the 2 groups. The median age was 67 years for both the darolutamide and placebo groups and most patients had a Gleason score of 8 or greater (77.6% vs 78.9%, respectively) and M1 stage (85.7% vs 86.5%) at initial diagnosis. At initial screening, patients in both groups were most likely to have M1b stage disease (79.4% vs 79.5%) and ALP levels equal to or above the upper limit of normal (55.5% each).

The effect of active therapy was consistent across patient subgroups, including by ALP level below the upper limit of normal (HR, 0.64; 95% CI, 0.56-0.85), and by metastatic stage at the time of diagnosis either de novo (HR, 0.71; 95% CI, 0.59-0.85) or recurrent (HR, 0.61; 95% CI, 0.35-1.05).

Moreover, darolutamide was associated with superior secondary outcomes. A significant delay in time to castration-resistant disease was noted in the darolutamide vs placebo groups, at NE (95% CI, NE-NE) vs 19.1 months (95% CI, 16.5-21.8), respectively (HR, 0.36; 95% CI, 0.30-0.42; P < .001). Darolutamide was also associated with increased time to pain progression at NE (95% CI, 30.5-NE) vs 27.5 months (95% CI, 22.0-36.1) with placebo (HR, 0.79; 95% CI, 0.66-0.95; P = .01). Time to first SSE was NE in both arms, but a statistically significant benefit with the darolutamide combination was noted (HR, 0.71; 95% CI, 0.54-0.94; P = .02).

Patients received fewer subsequent life-prolonging systemic antineoplastic therapies in the darolutamide arm (56.8%) vs the placebo arm (75.6%). Common subsequent therapies included abiraterone acetate (35.6% vs 46.9%, respectively), enzalutamide (Xtandi; 15.2% vs 27.3%), cabazitaxel (Jevtana; 18.1% vs 18.0%), and docetaxel (14.6% vs 18.0%). Notably, 66% of patients in the placebo arm went on to receive life-prolonging therapy with an AR pathway inhibitor. Time to first subsequent antineoplastic therapy was NE (95% CI, NE-NE) in the active therapy arm vs 25.3 months (95% CI, 23.1-28.8) in the placebo arm (HR, 0.39; 95% CI, 0.33-0.46; P < .001).

Rates of treatment-emergent adverse effects (AEs) were similar between arms, at 99.5% with the darolutamide regimen and 98.9% with placebo. “Consistent with prior clinical experience in other settings, darolutamide had a favorable safety profile. The rates of any treatment-emergent AE, serious AE, and AEs leading to permanent discontinuation of study treatment were similar between the darolutamide and the placebo groups,” Smith said.

Grade 3/4 AEs occurring with darolutamide and placebo included neutropenia (33.7% vs 34.2%, respectively), febrile neutropenia (7.8% vs 7.4%), hypertension (6.4% vs 3.2%), and anemia (4.8% vs 5.1%). After adjusting for differences in drug exposure, there was no difference in the occurrence of AEs of special interest for AR pathway inhibitors between groups, including events such as fatigue, bone fractures, rash, falls, hypertension, and cardiac disorders.

“Based on the results of ARASENS, we conclude that darolutamide in combination with ADT and docetaxel should become a new standard of care for the treatment of patients with [metastatic CSPC],” Smith concluded.

REFERENCES


Addition of Sacituzumab Govitecan to Pembrolizumab Produces Promising Antitumor Activity in Metastatic Urothelial Cancer

by HAYLEY VIRGIL

THE COMBINATION OF SACITUZUMAB govitecan-hziy (Trodelvy) and pembrolizumab (Keytruda) yielded promising antitumor activity in the second-line treatment of patients with checkpoint inhibitor-naïve metastatic urothelial cancer, according to cohort 3 results from the phase 2 TROPHY-U-01 trial (NCT03547973) presented at the 2022 Genitourinary Cancers Symposium.

At a median follow-up of 5.8 months, patients treated with the combination (n = 41) experienced an objective response rate (ORR) of 34% (95% CI, 20.1%-50.6%). Among responders, 1 patient experienced a complete response (CR) and 13 had a partial response (PR). Eleven patients (27%) achieved stable disease, with 4 (10%) patients experiencing stable disease for at least 6 months. Thus, the clinical benefit rate was 61% (95% CI, 44.5%-75.8%) (TABLE 1).1

“The data support further evaluation of antibody-drug conjugate (ADC)/checkpoint inhibitor combination therapy in metastatic urothelial cancer in the platinum-refractory setting and in earlier lines of therapy in a different patient population,” lead author Petros Grivas, MD, PhD, said during a presentation. “Additional follow-up for survival events and biomarkers are ongoing.” Grivas is clinical director of the Genitourinary Cancers Program and an associate professor in the Division of Medical Oncology at the University of Washington School of Medicine in Seattle.

Sacituzumab govitecan is a first-in-class Trop-2-directed ADC that is distinct from other ADCs as it has a high drug-to-antibody ratio (7.6:1), and internalization and enzymatic cleavage by tumor cell are not required for SN-38 liberation from the antibody.2

The agent approved by the FDA for the treatment of patients with metastatic triple-negative breast cancer who have received at least 2 prior chemotherapies—one in the metastatic setting—and for patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.3

As treatment options for patients with metastatic urothelial cancer remain limited and outcomes poor, with an estimated 5-year survival rate of less than 15%, investigators aimed to assess other safe and efficacious options to improve patient responses. Since ADCs, such as sacituzumab govitecan, have demonstrated the ability to induce immunogenic cell death and possibly result in additive or synergistic activity when combined with checkpoint inhibitors, investigators pursued the hypothesis that this may be a valuable combination strategy capable of providing benefit to patients with metastatic disease.

In cohort 3 of the registrational, open-label multicohort study, investigators planned to enroll up to 61 patients who were checkpoint inhibitor naïve with progressive disease following treatment with platinum-based therapies. Patients enrolled to this cohort received sacituzumab govitecan at a dose of 10 mg/kg on days 1 and 8 every 21 days and 200 mg of pembrolizumab on day 1 every 21 days. Treatment continued until patients experienced unacceptable toxicity or disease progression. Patients needed to be 18 years or older with an ECOG performance status of 0 or 1. Additionally, a creatinine clearance of 30 mL per minute or higher and adequate hepatic function were required.

As for key exclusion criteria, patients could not have immunodeficiency, active hepatitis B or C infection, active secondary malignancy, or active brain metastases.

The median age of evaluable patients was 67 years (range, 46-86). Most patients had an ECOG performance status of 1 (61%). At baseline, 9 patients (22%) had locoregional tumor stage and 32 patients (78%) had distant metastasis tumor stage. Twenty-eight patients (68%) had a visceral site of disease at baseline—which included 12 patients (29%) having liver metastasis—compared with 13 patients (32%) who did not. All evaluable patients had up to 2 ant canc er chemotherapy regimens. Twenty-eight patients (68%) received prior cisplatin and 12 patients (29%) received prior carboplatin.

In total, 24%, 49%, and 27% of patients had a Bellmunt risk factor of 0, 1, and 2, respectively.Investigators also reported 49% of patients underwent neoadjuvant or adjuvant therapy with a median time from end of most recent prior systemic therapy to screening date of 6.8 months. This compares with the 51% of patients who underwent metastatic therapy with a median time from end of most recent prior systemic therapy to screening date of 1.6 months. In terms of best response to prior systemic therapy in the metastatic setting, 1 patient (2%) had a previous CR, 2 patients (5%) had a PR, 11 patients (27%) had SD, and 6 patients (15%) had PD.

The study’s primary end point was ORR by investigator review per RECIST 1.1 criteria, with key secondary end points including safety and tolerability, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

When examining ORR by subgroup, investigators reported that patients with an ECOG performance status of 0 and 1 showed a rate of 43.8% (19.7%-70.12%) and 28% (95% CI,

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**TABLE 1. Efficacy Outcomes in Cohort 3 of the TROPHY-U-01 Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sacituzumab govitecan plus pembrolizumab (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>34% (20.1%-50.6%)</td>
</tr>
<tr>
<td>PR</td>
<td>2%</td>
</tr>
<tr>
<td>SD</td>
<td>32%</td>
</tr>
<tr>
<td>SD ≥ 6 months</td>
<td>27%</td>
</tr>
<tr>
<td>PD</td>
<td>10%</td>
</tr>
<tr>
<td>PD not assessed</td>
<td>29%</td>
</tr>
<tr>
<td>CBR</td>
<td>61% (44.5%-75.8%)</td>
</tr>
<tr>
<td>Median time to follow-up, months</td>
<td>5.8</td>
</tr>
<tr>
<td>Median time to response, months (range)</td>
<td>2 (1.3-2.8)</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>2 (1.3-2.8)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.5 (1.7-NR)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>6.1 (NR-NR)</td>
</tr>
</tbody>
</table>

CBR, clinical benefit rate; CR, complete response; DOR, duration of response; NA, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Neoadjuvant Enfortumab Vedotin Demonstrates Encouraging Activity in Cisplatin-Ineligible MIBC

**ENFORTUMAB VEDOTIN-EJFV (PADCEV)** produced promising antitumor activity as neoadjuvant treatment for patients with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin, according to preliminary findings from cohort H of the phase 1b/2 EV-103 trial (NCT03288545) presented during the 2022 Genitourinary Cancers Symposium.

Notably, investigators reported a pathological complete response (pCR) rate of 36.4% (95% CI, 17.2%-59.3%) and a pathological downstaging (pDS) rate of 50% (95% CI, 28.2%-71.8%) in patients who received neoadjuvant enfortumab vedotin (n = 22).

"This first disclosure of data supports the ongoing phase 2 and 3 [trials] evaluating enfortumab vedotin alone or in combination with pembrolizumab [Keytruda] in MIBC," said Daniel P. Petrylak, MD, professor of medical oncology and urology at Yale Cancer Center in New Haven, Connecticut, in reference to cohort H of the ongoing EV-103 trial.

Neoadjuvant treatment options for patients with MIBC who are cisplatin ineligible are lacking in survival benefit when administered prior to standard radical cystectomy and pelvic lymph node dissection. For patients who are eligible for cisplatin-based chemotherapy, pCR rates range from 36% to 42%.

Enfortumab vedotin previously demonstrated promising safety and efficacy data among cisplatin-ineligible patients with previously treated advanced urothelial carcinoma in the phase 3 EV-301 trial (NCT03474107). The FDA granted full approval to the agent in 2021 following data that showed improved overall survival (OS) vs chemotherapy and a tolerable safety profile in patients with advanced urothelial carcinoma.

Additional findings from the study indicated that 63% of patients experienced tumor shrinkage. Patients had a median time to response of 2 months (range, 1.3-2.8). The median DOR was not yet reached (NR; 95% CI, 2.80-not available). The median PFS was 5.5 months (95% CI, 1.7-NR) and the median OS was NR.

The most common any-grade adverse effects (AEs) in cohort 3 were diarrhea (76%), nausea (59%), and anemia (56%). Commonly reported grade 3 or higher AEs were neutropenia (27%), diarrhea (24%), anemia (20%), and leukopenia (20%).

The median duration of treatment was 4 months with sacituzumab govitecan and 3.5 months with pembrolizumab. Sixty-eight percent of patients permanently discontinued treatment and 32% remained on treatment at the time of data cutoff. Patients who discontinued did so because of progressive disease (51%), withdrawal of consent (5%), AEs (3%), or treatment delays of more than 5 weeks (7%).

No new safety signals were reported. The most common any grade treatment-related AEs (TRAEs) were diarrhea (71%), nausea (54%), and neutropenia (44%). Grade 3 or 4 TRAEs occurred in 59% of patients, with 39% of patients discontinuing sacituzumab govitecan treatment because of TRAEs. No treatment-related deaths occurred.

Twenty-five percent of patients required a steroid to combat an immune-related AE, with 15% of patients requiring topical and 10% requiring oral steroids for diarrhea, pruritis, or maculopapular rash. Investigators also reported that 29% of patients required granuloma macrophage colony-stimulating factor; this was not an increased rate.

"[Other] TROPHY-U-01 cohorts are being assessed. We have cohort 2 looking at sacituzumab govitecan as a single agent after checkpoint inhibition and cohorts 4 and 5 evaluating sacituzumab govitecan in combination with cisplatin plus or minus avelumab [Bavencio] as induction therapy followed by avelumab [switch maintenance therapy]," Grivas said.

**For a full list of references, see the article at OncLive.com**

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**TABLE 2. ORR by Subgroup in Cohort 3 of the TROPHY-U-01 Trial**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ORR Sacituzumab govitecan plus pembrolizumab (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>40% (12.16%-73.76%)</td>
</tr>
<tr>
<td>50 to 64 years</td>
<td>35.7% (18.64%-55.93%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>40% (12.07%-73.76%)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0 (95% CI)</td>
<td>43.8% (19.75%-70.12%)</td>
</tr>
<tr>
<td>1 (95% CI)</td>
<td>28% (12.07%-49.39%)</td>
</tr>
<tr>
<td>Baseline visceral metastasis involvement</td>
<td></td>
</tr>
<tr>
<td>Yes (95% CI)</td>
<td>35.7% (18.64%-55.93%)</td>
</tr>
<tr>
<td>No (95% CI)</td>
<td>30.8% (9.09%-61.43%)</td>
</tr>
<tr>
<td>Baseline visceral metastasis and liver involvement</td>
<td></td>
</tr>
<tr>
<td>Yes (95% CI)</td>
<td>41.7% (15.17%-72.33%)</td>
</tr>
<tr>
<td>No (95% CI)</td>
<td>31% (15.28%-50.83%)</td>
</tr>
<tr>
<td>Bellmunt risk factor groups</td>
<td></td>
</tr>
<tr>
<td>0 (95% CI)</td>
<td>40% (12.16%-73.76%)</td>
</tr>
<tr>
<td>1 (95% CI)</td>
<td>35% (15.39%-59.22%)</td>
</tr>
<tr>
<td>2 (95% CI)</td>
<td>27.3% (6.02%-60.97%)</td>
</tr>
</tbody>
</table>

1 NA, not available; ORR, objective response rate.
carcinoma previously treated with chemotherapy and a PD-1 or PD-L1 inhibitor. In cohort H of the EV-103 trial, patients received 1.25 mg/kg of neoadjuvant enfortumab vedotin monotherapy on days 1 and 8 for three 21-day cycles. Within 4 weeks of treatment, patients underwent radical cystectomy plus pelvic lymph node dissection followed by imaging every 12 weeks for the first 2 years and then every 24 weeks thereafter.

In addition to cisplatin ineligibility, inclusion criteria required patients to have clinically staged T2N0 to T4aN0 disease and have no upper tract or urethral tumors. Additionally, a urothelial carcinoma histology of greater than 50% was required. Patients also needed to have an ECOG performance status of 0 to 2, be medically fit for radical cystectomy plus pelvic lymph node dissection, and have undergone transurethral resection of a bladder tumor within 90 days of the first day of cycle 1.

The median enrollment time from diagnosis was 1.6 months (range, 1-3). Enrolled patients had a median age of 74.5 years (range, 56-81). Most patients had an ECOG performance status of 0 (59.1%), followed by 1 (36.4%) and 2 (4.5%). Additionally, most patients had clinically staged T2N0 disease (68.2%), followed by T3N0 (27.3%) and T4aN0 (4.5%). Fifteen patients (68.2%) had transitional cell carcinoma (TCC) only, 3 patients (13.6%) had TCC with squamous differentiation, and 4 patients (18.2%) had TCC with other histological variants, such as adenocarcinoma (n = 1; 4.5%), micropapillary (n = 2; 9.1%), and sarcomatoid (n = 1; 4.5%).

The most common reasons for cisplatin ineligibility were creatine clearance between 30 and 60 mL per minute (50%) and grade 2 or greater hearing loss (40%).

The median duration of neoadjuvant treatment with enfortumab vedotin was 2.1 months (range, 0.7-2.3). Nineteen patients (86%) completed all 3 cycles of neoadjuvant therapy. The 3 deaths that occurred on the study were due to acute kidney injury, cardiac arrest related to radical cystectomy and pelvic lymph node dissection, and pulmonary embolism related to radical cystectomy and pelvic lymph node dissection. Notably, all enrolled patients underwent surgery without delay. The median time from the end of the neoadjuvant therapy to radical cystectomy and pelvic lymph node dissection was 16 months (range, 1.0-2.7).

The primary end point was pCR by central pathology review. Secondary end points included pDS by central review, event-free survival, disease-free survival, OS, safety, patient-reported outcomes, and biomarker assessment. pCR was defined as absence of any viable tumor tissue, specifically, ypT0 and N0, and pDS was defined as presence of ypT0, ypTis, ypTa, ypT1, and N0.

Any-grade treatment-emergent adverse effects (TEAEs) were observed in all patients, with common TEAEs including fatigue (45.5%), alopecia (36.4%), dysgeusia (36.4%), diarrhea (27.3%), nausea (27.3%), peripheral sensory neuropathy (27.3%), dry eye (22.7%), and maculopapular rash (22.7%).

The overall incidence of grade 3 or higher TEAEs was low. Specifically, 4 patients experienced grade 3 or higher TEAEs, including asthenia, dehydration, erythema multiforme, hyperglycemia, postprocedural urine leak, maculopapular rash, and small intestinal obstruction. No grade 4 TEAEs or deaths were reported.

There were 3 (13.6%) observed TEAEs that led to enfortumab vedotin dose interruption; 2 delays were due to grade 1 diarrhea and grade 2 fatigue, and one resulted in elimination. Additionally, there were 2 (9.1%) reported grade 2 TEAEs—dysgeusia and diarrhea—that led to dose reduction and 3 (13.6%) reported grade 3 TEAEs—dehydration, erythema multiforme, and maculopapular rash—that led to dose discontinuation. Notably, there were no dose reductions due to peripheral neuropathy (TABLE 1).

Overall, no new safety signals were identified. Most AEs of special interest were grade 1 and 2 and resolved. Any grade AEs of interest included peripheral neuropathy (36.4%), skin reaction (63.6%), nonfasting hyperglycemia (22.7%), ocular disorder (40.9%), and infusion-related reactions (9.1%). Grade 3 or higher AEs of special interest were skin reactions (9.1%) and hyperglycemia (13.6%). Notably, there was no preexisting diabetes mellitus for the 5 patients who experienced grade 1 or 2 nonfasting hyperglycemia.

“The observed safety profile of neoadjuvant enfortumab vedotin monotherapy in patients with cisplatin-ineligible MIBC is consistent with the known AE profile of enfortumab vedotin in other settings,” Petrylak said.

REFERENCES

More on OncLive.com
In an exclusive interview with OncLive®, Daniel P. Petrylak, MD, discusses the utilization of enfortumab vedotin-efjv (Padcev) in patients with muscle-invasive bladder cancer (MIBC). In a review of results from cohort H of the phase 1b/2 EV-103 trial (NCT03218545), Petrylak commented on the tumor reduction and pathologic complete response observed with 3 cycles of neoadjuvant enfortumab vedotin. “This does seem to have significant effectiveness in this group of patients,” Petrylak said.

Watch Now
Scan the QR code or go to bit.ly/3Jb57if
Indication
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Safety Information

Warnings and Precautions

- **Diarrhea**: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
Monitor ALT, AST, and bilirubin prior to starting TUKYSA.

**Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

**Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

### Important Safety Information

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

**Adverse Reactions**

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

In combination with trastuzumab + capecitabine

**TUKYSA extended overall survival**

**RAISING THE STANDARD FOR SURVIVAL**

**4.5 MONTH IMPROVEMENT IN MEDIAN OS**

TUKYSA reduced the risk of disease progression or death from any cause in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death due to disease progression or death1 and TRAEs leading to treatment discontinuation). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

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Hepatotoxicity:
• If diarrhea occurs, administer antidiarrheal treatment as
• Diarrhea:

Important Safety Information

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Adverse reactions led to treatment discontinuation in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, hypotension, acute kidney injury, and death.

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were:
• Diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), dehydration, hypotension, acute kidney injury, and death.

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients were increased ALT, increased AST, increased GGT, decreased potassium, increased creatinine, decreased albumin.

Patients Alive (%)

Control arm

TUKYSA arm

PFS AT 12 MONTHS

Control arm: 12%

TUKYSA arm: 33%

~3x as many patients were progression-free

PFS at 12 months

median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.8 months (95% CI: 4.2-7.1) in the control arm

HR = 0.54 (95% CI: 0.42-0.71); P = <0.00001

Median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.8 months (95% CI: 4.2-7.1) in the control arm

PFS at 12 months

median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.8 months (95% CI: 4.2-7.1) in the control arm

HR = 0.54 (95% CI: 0.42-0.71); P = <0.00001

Lab Abnormalities

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST. The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

Drug Interactions

• Strong CYP3A/Moderate CYP2C8 Inducers: Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
• Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
• CYP3A Substrates: Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
• P-gp Substrates: Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

Use in Specific Populations

• Lactation: Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
• Renal Impairment: Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
• Hepatic Impairment: Reduce the dose of TUKYSA for patients with severe (Child–Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References:
TUKYSA® (tucatinib) tablets, for oral use
Brief summary of Prescribing Information (PI). See full PI. Rx Only

INDICATIONS AND USAGE
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSAGE AND ADMINISTRATION
Recommended Dosage
The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time. When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions
The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

**Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions**

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Recommended TUKYSA Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>250 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>200 mg orally twice daily</td>
</tr>
<tr>
<td>Third</td>
<td>150 mg orally twice daily</td>
</tr>
</tbody>
</table>

Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

**Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions**

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 3 without anti-diarrhea treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 with anti-diarrhea treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2 bilirubin (≥1.5 to 3 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 ALT or AST (≥ 5 to 20 × ULN) or Grade 3 bilirubin (≥ 3 to 10 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4 ALT or AST (≥ 20 × ULN) or Grade 4 bilirubin (≥ 10 × ULN)</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>ALT or AST &gt; 3 × ULN AND Bilirubin &gt; 2 × ULN</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Other adverse reactions

| Grade 3 | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level. |
| Grade 4 | Permanently discontinue TUKYSA. |

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

**Dosage Modifications for Severe Hepatic Impairment:** For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

**Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors:** Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor.

**CONTRAINDICATIONS**
None.

**WARNINGS AND PRECAUTIONS**

**Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 8% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

**Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

**Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential that the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information for trastuzumab and capecitabine for pregnancy and contraception information.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

**HER2-Positive Metastatic Breast Cancer (HER2CLIMB)**

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm.

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and sepsis (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-planter erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

**Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>All 3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>3.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-planter erythrodysesthesia syndrome</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Rash1</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20</td>
<td>0.5</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

Strong CYP3A Inducers or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inhibitor decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inhibitor.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates.

where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Lactation

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for information. There are data on the presence of tucatinib or its metabolites in human or animal 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 with TUKYSA and for at least 1 week after the last dose.

Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

Prepregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

Contraception:

Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA for at least 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Infertility: Based on findings from animal studies, TUKYSA may impair male and female fertility.

Pediatric Use: The safety and effectiveness of TUKYSA in pediatric patients have not been established.

Geriatric Use: In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in these receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

Renal Impairment: The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance (CLcr) 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
<th>All Grades</th>
<th>Grades ≥3</th>
<th>All Grades</th>
<th>Grades ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59</td>
<td>3.3</td>
<td>51</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Decreased phosphate</td>
<td>57</td>
<td>8</td>
<td>45</td>
<td>7</td>
<td></td>
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<tr>
<td>Increased bilirubin</td>
<td>47</td>
<td>1.5</td>
<td>30</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
<td>8</td>
<td>27</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>43</td>
<td>6</td>
<td>25</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>40</td>
<td>0.8</td>
<td>25</td>
<td>0.5</td>
<td></td>
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</tr>
<tr>
<td>Decreased potassium</td>
<td>36</td>
<td>6</td>
<td>31</td>
<td>5</td>
<td></td>
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<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>28</td>
<td>2.5</td>
<td>23</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>26</td>
<td>0.5</td>
<td>17</td>
<td>0</td>
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</tr>
</tbody>
</table>

Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NC-CTCAE v4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NC-CTCAE v5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v4.03.

TUKYSA and its logo, and Seagen and © are US registered trademarks of Seagen Inc. © 2021 Seagen Inc., Bothell, WA 98021 All rights reserved Printed in USA REF-5155(1) 4/20
Obe-cel May Mark Additional Treatment Option for R/R B-ALL

by KYLE DOHERTY

LONG-TERM REMISSIONS FOR ADULT patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) have eluded investigators using combination chemotherapy approaches. Despite initial responses to treatment, more than 50% of patients will ultimately experience disease progression, which is associated with poor prognosis.1 Efforts are underway to evaluate novel, durable treatment options for this patient population in the phase 1b/2 FELIX trial (NCT04404660) evaluating obecabtagene autoleucel (obe-cel; AUTO1), a novel, second-generation chimeric antigen receptor (CAR) product.

CD19-directed CAR T-cell products such as tisagenlecleucel (Kymriah) initially demonstrated efficacy with durable remissions and long-term persistence; however, the patient population was pediatric patients with relapsed or refractory B-ALL, who account for upward of 75% of all B-ALL cases.2,3 Tisagenlecleucel was approved by the FDA on August 30, 2017, for the treatment of patients up to age 25 with B-ALL after 2 prior lines of therapy, or after failure or intolerance of a second-generation tyrosine kinase inhibitor.4

In October 2021, the FDA approved brexucabtagene autoleucel (Tecartus), the first CD19-directed CAR T-cell therapy for use in adult patients with relapsed/refractory B-ALL, including after the first relapse.

Investigators hope obe-cel will provide an additional CD19-directed CAR T-cell option to their arsenal.5,6 Obe-cel’s unique mechanism of action mimics physiological T-cell receptor interactions. The agent has a lower affinity for CD19 than similar CAR T products. This design helps to avoid CAR T-cell over-activation and exhaustion. Further, the half-life of the target interaction of obe-cel is 9.8 seconds compared with 21 minutes with tisagenlecleucel.5,6 In 2019, the FDA granted obe-cel an orphan drug designation.7,8

“With obe-cel, [investigators] tried to develop a low-affinity CD19 binder that would allow the CAR T cells to rapidly bind and then release,” Bijal Shah, MD, MS, an associate member of the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida, said in an interview with OncologyLive.9 “The hope was this would do 2 things: the first was that it would decrease some of the toxicity associated with CAR T-cell therapy, specifically cytokine release syndrome [CRS] and neurologic adverse effects [AEs]. The second, that it would improve the health of the T cell and limit T-cell exhaustion so the T cells can stay active for a longer period.”

OBE-CEL DEMONSTRATES EARLY EFFICACY

Investigators previously evaluated obe-cel for safety and initial efficacy in the phase 1, single-arm, multicenter ALLCAR19 trial (NCT02935257). A total of 25 patients with relapsed/refractory B-ALL aged 16 or older underwent leukapheresis. The median age of participants was 41.5 years (range, 18-62) and a majority of patients were male (65%). Patients had a median of 3 (range, 2-6) prior lines of treatment, including inotuzumab ozogamicin (Besponsa; 50%) and blinatumomab (Blincyto; 25%). Most had also received prior allogeneic hematopoietic stem cell transplantation (65%).9,10

Twenty-four CAR T-cell products were manufactured, and 20 patients were ultimately infused with obe-cel. Prior to infusion, patients underwent lymphodepletion with 30 mg/m² of intravenous fludarabine over 3 days and a single 60-mg/kg dose of cyclophosphamide. Obe-cel was given in a split-dose schedule; patients with more than 20% blasts received 10 × 10⁶ CAR T cells and patients with blasts of 20% or less received 100 × 10⁶ CAR T cells on day 0. The second dose was given at an interval of 9 days for a total dose of 410 × 10⁶ CAR T cells.

Findings showed that the event-free survival (EFS) rates for patients who received obe-cel were 68.3% (95% CI, 42.4%-84.4%) at 6 months and 48.3% (95% CI, 23.1%-69.7%) at 12 months when measured by morphologic relapse criteria. This response was maintained at 24 months with an EFS rate of 68.3% (95% CI, 23.1%-69.7%). The overall survival (OS) rates were 69.1% (95% CI, 43.6%-84.8%), 63.8% (95% CI, 38.6%-80.8%), and 58.0% (95% CI, 33.1%-76.4%) at 6, 12, and 24 months, respectively. Additionally, 85% (95% CI, 62.1%-96.7%) of patients with a response (n = 20) achieved minimal residual disease (MRD)-negative complete response (CR) at month 1, and 70% (95% CI, 45.7%-88.1%) experienced an ongoing MRD-negative CR at month 3.

“What [investigators] are seeing with follow-up is that many of these responses are maintained,” Shah said. “The EFS looks like it is going to be about 1 year [based on the curves], and that is outstanding; it is a signal for an effective CAR T-cell product. The CAR T cells also seem to persist over time, which seems to be encouraging in terms of helping to mitigate against subsequent relapse. We need to prove that, but the early data are certainly promising.”

In terms of safety, no cytokine release syndrome (CRS) events of grade 3 or higher were reported. Grade 1 and 2 CRS events were observed in 15% and 30% of patients, respectively. Investigators reported grade 4 thrombocytopenia among 70% of patients, and grade 1/2 and grade 3 in a small portion of patients (15%). All patients experienced an infection of any grade.

The tolerable safety profile of obe-cel coupled with high remission rates and persistence for adult patients with relapsed/refractory B-ALL provided the rationale for the FELIX trial.

During the 63rd American Society of Hematology Annual Meeting and Exposition, investigators presented initial efficacy and safety data from the phase 1b part of FELIX. At the data cutoff date of September 13, 2021, results showed that among the 16 patients who had been treated with obe-cel, the overall response rate (ORR) was 75% (95% CI, 48%-93%). At 1 month after obe-cel administration, 12 patients had achieved a CR or CR with incomplete recovery of counts, which was comparable with 85% of patients at the same point in the ALLCAR19 study.11

In terms of safety, CRS of any grade was reported in 56% of patients; no grade 3 or greater CRS events were reported. Neurotoxicity of any grade was seen in 13% of patients, with 6% experiencing an event of grade 3 or higher. Grade 3 immune effector cell-associated neurotoxicity syndrome was reported in 1 patient (TABLE).9,10

<table>
<thead>
<tr>
<th>TABLE. Initial Safety Data in the FELIX Trial</th>
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</thead>
<tbody>
<tr>
<td>Maximum grade toxicity</td>
<td>Percentage of patients (n = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CRS event</td>
<td>56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS ≥ grade 3</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any neurotoxicity</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity ≥ grade 3</td>
<td>6%</td>
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</tbody>
</table>

CRS, cytokine release syndrome.
Therapeutics, the manufacturer of obe-cel, is enrolling adult patients with relapsed or refractory B-ALL, with a target total of approximately 185 patients. All enrolled patients will have less than 5% bone marrow blasts. Autolus Therapeutics, the manufacturer of obe-cel, expects to present data from the pivotal phase 2 portion of the study in 2022.

**DETAILS OF THE FELIX TRIAL**

The open label, multicenter, single-arm study is enrolling adult patients with relapsed or refractory B-ALL, with a target total of approximately 185 patients. All enrolled patients will sequentially complete screening, leukapheresis, preconditioning with cyclophosphamide and fludarabine chemotherapy, treatment, and follow-up stages. A total target dose of $10^6$ to $10^7$ CAR T cells as a split dose on day 1 and day 10 is aspirated.

The median age of patients included in the report was 42 years. Most patients had bone marrow blasts over 20% and had previously been treated with blinatumomab (75% and 56%, respectively). Twenty-five percent of patients had less than 5% bone marrow blasts. Autolus Therapeutics, the manufacturer of obe-cel, presented data from the pivotal phase 2 portion of the study in 2022.

**REFERENCES**


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**"What" distinguishes the FELIX trial is [that it is using] fractionated infusion...This was to improve safety, particularly as they went up on the total cell dose. [Investigators] did succeed in that regard, and this set the stage for other approaches looking at fractionated infusion.”**

— BIJAL SHAH, MD, MS
The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients² ³

Consistent results with or without prior adjuvant chemotherapy² ³

- Patients in the ADAURA trial are treated with ORAL TAGRISSO FOR 3 YEARS or until disease recurrence or unacceptable toxicity³

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

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

*Median DFS was not reached for TAGRISSO (95% CI: 58.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.¹

¹Control arm=placebo.

²Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).²

²Hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

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References: 1. 


‡
• TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer

INDICATION

ADJUVANT TAGRISSO: DELIVERING
TAGRISSO demonstrated extraordinary disease-free survival FOR RESECTABLE EGFR m NSCLC THE FIRST EVER TARGETED THERAPY in resected EGFRm NSCLC patients

Control arm=placebo. Consistent results with or without prior adjuvant chemotherapy‡

• Patients in the

NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive;

TAGRISSO if ILD is confirmed respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue as detected by an FDA-approved test (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations,

DFS Probability

0.0

0.6

0.2

1.0

0

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

6 12 18 24 30 36 42 48 54

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Find out more at www.TagrissoResults.com

SELECT SAFETY INFORMATION

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

- Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO

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

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

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

- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

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

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

Adjacent treatment of EGF Receptor Mutations-Positive Non-Small Cell Lung Cancer (NSCLC) TARGRSO is indicated as adjacent therapy after tumor regression in adult patients with non-small cell lung cancer whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC TARGRSO is indicated for the first-line treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on an EGFR tyrosine kinase inhibitor (TKI) therapy; TARGISRO is FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1) in the full Prescribing Information].

DOSE AND ADMINISTRATION

Patient Selection

Select patients with resectable tumors for the adjacent treatment of NCLC with TARGISRO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimen [see Clinical Studies (14) in the full Prescribing Information].

Select patients for the first-line treatment of metastatic EGFR T790M mutation-positive NSCLC based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimen. [see Clinical Studies (14) in the full Prescribing Information]. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TARGISRO in the first-line treatment of adult patients with untreated NSCLC whose tumors have epidermal growth factor receptor (EGFR) mutations. Select patients for the treatment of NSCLC whose tumors have epidermal growth factor receptor (EGFR) mutations who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Dosage Information

TARGISRO is not recommended for patients with history of Grade 4 QTc interval prolongation or have a personal or family history of long QT syndrome. Obtain an electrocardiogram (ECG) for patients in whom the QTc interval is greater than 450 ms or who have a known history of QT prolongation. Patients with a QTc interval of greater than 500 ms on electrocardiogram are not recommended to receive TARGISRO.

ADVERSE REACTIONS

Table 1. Recommended Dosage Modification for TARGISRO

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>(see Warnings and Precautions (5.1) in the full Prescribing Information)</td>
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<td>Without TARGISRO (qt=500 msc) or more than 2 exposures (QTcF)</td>
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<td>QTc Interval greater than 500 ms or more than 2 exposures (QTcF)</td>
<td>Without TARGISRO (qt=500 msc) or more than 2 exposures (QTcF)</td>
<td></td>
</tr>
<tr>
<td>QTc Interval greater than 500 ms or more than 2 exposures (QTcF)</td>
<td>Without TARGISRO (qt=500 msc) or more than 2 exposures (QTcF)</td>
<td></td>
</tr>
</tbody>
</table>
| QTc Interval greater than 500 ms or more than 2 exposures (QTcF) | Without T...
Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 22% with the chemotherapy comparator, with no single adverse reaction reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a total adverse reaction (LD/pneumonitis).

Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.0%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was aspartate aminotransferase (AST) (3%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
<td>1.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33</td>
<td>2.3</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>32</td>
<td>3.9</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>44</td>
<td>2.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>Metabolic</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The safety of TAGRISSO was evaluated in AURA1, a multicenter international open label randomized (2:1) controlled trial conducted in 449 patients with untreated or metastatic EGFR TKI mutation-positive NSCLC who had progressive disease following first line EGFR TKI treatment. A total of 279 patients received TAGRISSO 80 mg orally once daily until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment. A total of 138 patients received pembrolizumab plus either carboplatin or paclitaxel every 3 weeks for up to 4 cycles; patients without disease progression after 4 cycles of chemotherapy could continue maintenance pembrolizumab until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment. Left Ventricular Ejection Fraction (LVEF) was evaluated at screening and every 12 weeks. The median duration of treatment was 8.1 months for 39% of patients treated with TAGRISSO and 4.3 months for chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 (58%), female (45%), Asian (8%), never smokers (85%), and ECOG PS 0 or 1 (100%).

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISO dose by 50% when co-administering with a strong CYP3A4 inducer. The current use of concomitant drugs is unavoidable [see Dosage and Administration (2.4) in the full Prescribing Information]. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inhibitors.

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

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

Drugs That Prolong the QTc Interval
The effect of osimertinib on other drugs known to prolong the QTc interval with TAGRISSO is not known. Avoid concomitant administration of drugs known to prolong the QTc interval with known risk of torsades de pointes. If not avoidable to avoid co-administration of such drugs, conduct periodic ECG monitoring [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on data from animal studies and its mechanism of action [see Clinical Pharmacology (12.1) in the full Prescribing Information], TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on osimertinib use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryotoxicity and reduced fetal growth at plasma exposures 3-8 times the exposure at the recommended clinical dose (see Data). Advise pregnant women of the potential risk of a fetus.

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

**Animal Data**

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20), which produced plasma exposure of approximately 1.5-2 times the osimertinib systemic clearance, there was no evidence of fetal toxicity or teratogenic effects. However, during organogenesis on day 20 of gestation, when administered to pregnant rats prior to implantation, the expected clinical dose of osimertinib was attained. 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.

**Artifacts**

Increased AST 22 1.1 43 4.1

Hypokalemia† 9 1.4 18 1.5

† No grade 4 events were reported.

† Includes rash, redness, rash systemic, rash rash, oral ulcer, pruritus, oral ulcer, pruritus.

† Includes dry skin, skin fissures, xerosis, xeroderma.

† Includes dry skin, skin rashes, dry skin, pruritus, xerosis.

† Includes dry skin, skin rash, rash systemic, rash, oral ulcer, oral ulcer, pruritus, oral ulcer.

† Includes rash, redness, rash systemic, rash, oral ulcer, pruritus, oral ulcer.

† Includes rash, redness, rash systemic, rash, oral ulcer, oral ulcer, pruritus, oral ulcer.

† Includes pruritus, pruritus generalized, erythema, pruritus.

† Includes rash, redness, rash systemic, rash, oral ulcer, oral ulcer, pruritus, oral ulcer.

† Includes rash, redness, rash systemic, rash, oral ulcer, oral ulcer, pruritus, oral ulcer.

† Includes rash, redness, rash systemic, rash, oral ulcer, oral ulcer, pruritus, oral ulcer.

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† Include...
Immunotherapy Could Play a Role in RCC After Progression

by CHRIS RYAN

TREATMENT WITH A TYROSINE kinase inhibitor (TKI) remains the standard of care for patients with metastatic renal cell carcinoma (RCC) who progress following immunotherapy in the frontline setting. However, ongoing clinical trials are investigating whether immunotherapy agents have a role after progression, according to Moshe Ornstein, MD, MA.

Ornstein noted that pending data from 2 studies could help answer a pivotal question in the treatment space for RCC post immunotherapy progression: CONTACT-03 (NCT04338269) is exploring the combination of cabozantinib (Cabometasix) plus atezolizumab (Tecentriq) vs cabozantinib monotherapy, and TiNivo-2 (NCT04987203) is investigating tivozanib (Fotivda) plus nivolumab (Opdivo) vs tivozanib monotherapy.

“We have seen tremendous progress in the treatment of patients with metastatic clear cell RCC who receive immunotherapy-based combinations up front,” Ornstein said. “We have ipilimumab [Yervoy] and nivolumab, axitinib [Inlyta] and pembrolizumab [Keytruda], cabozantinib and nivolumab, lenvatinib [Lenvima] and pembrolizumab, etc. [We have] all these immunotherapy-based combinations, but a real question that remains unanswered in the field is what is the role of immunotherapy [is] in patients whose cancer has progressed having already received immunotherapy.”

In an interview with OncologyLive® during the American Society of Clinical Oncology 2022 Genitourinary Cancers Symposium, Ornstein, a genitourinary medical oncologist at the Taussig Cancer Institute at Cleveland Clinic in Ohio, discussed the clinical trials exploring second-line immunotherapy in patients who have progressed on immunotherapy, highlighting key trial data and other pressing areas of need for research in RCC.

Q What was the rationale for the NeoAvAx trial (NCT03341845), 1 which evaluated neoadjuvant avelumab (Bavencio) plus axitinib in patients with localized RCC who were at high risk for relapse following nephrectomy?

There is a lot of talk about adjuvant therapy for patients who are at high risk of recurrence after their kidney cancer is removed, [and] a lot of rationale to give therapy before surgery, as well. [One] of the reasons to give therapy before surgery is to downsize a tumor to make the surgery either easier or to allow for additional nephron sparing.

Another reason to give therapy before surgery, especially immunotherapy before surgery, is that, theoretically, giving immunotherapy when the primary tumor is in place produces better results. Data from other tumor types [show that] giving immunotherapy before surgery can improve disease-free survival [DFS] compared with after surgery, and that is what this phase 2 trial did with axitinib and avelumab. Axitinib is a VEGFR TKI, and avelumab is a PD-L1 inhibitor. Combinations of these treatment classes are approved for patients with metastatic kidney cancer.

We know axitinib and avelumab, when combined, are active for patients with metastatic kidney cancer. The question is if we selected patients in the neoadjuvant setting, [would] there be a response in those patients as well. [This study included] patients who were at high risk of relapse, patients who had clinically node-positive disease, a high T stage, [or] a high Fuhrman grade, and treated them with 6 doses of avelumab. [This] was given every other week for 6 cycles, so basically 12 weeks of treatment before surgery. Axitinib, which is a pill, was given at the standard dosing with dose-escalation parameters built into the trial.

The primary end point [was] objective response rate (ORR)—specifically, if patients get this combination before surgery, what ... rate of patients have a 30% tumor burden decrease at the time of surgery. Secondary end points [included] DFS, overall survival [OS], safety, and tolerability.

A total of 40 patients were enrolled in the trial. The median age of these patients [was] what we generally see in our kidney cancer clinics, 63 years. [It was] predominantly a male population, accounting for 70% of the patients. The population did span the range of high-risk categories: 43% of the patients had node-positive disease, 20% of tumors were T4, and 28% had Fuhrman grade 3 or 4 disease.

The high-level results are as follows: 12 of the 40 patients [30%] had what is considered a partial response. The ORR was 30%. Interestingly, 83% of the patients who had a response remained disease free at the time of study follow-up. The median DFS and median OS were not reached. However, at a median follow-up of close to 2 years, recurrence occurred only in approximately one-third of patients.

Q What were the biggest safety takeaway from the trial?

Any time we talk about a neoadjuvant or an adjuvant trial in patients who have localized kidney cancer, we must take the efficacy in the context of the toxicity. For patients who have metastatic kidney cancer, most are not going to be cured. We will accept the higher rate of toxicity. But when we talk about a patient who has localized kidney cancer, even though many of those patients will have disease recurrence, many of them are going to be cured without treatment. We must set the bar for toxicity a little lower for what we are willing to accept.

What is important in this trial is that this combination before surgery was well tolerated. There were not any unexpected toxicities; all serious adverse [effects] were resolved. Also important in the neoadjuvant setting is the toxicity at the time of surgery, and there did not appear to be any notable surgical complications.

There is activity for this combination prior to surgery, and it does not come with worry-some toxicity. Although it is not a standard of care to give this combination prior to surgery for patients who have localized kidney cancer, it does establish a standard where this can be done safely if it is needed in the right patient. There are some data now to support its use, but it is not a standard of care.

Q What were the key highlights from the 30-month follow-up of the phase 3 KEYNOTE-564 trial (NCT03142334)?

KEYNOTE-564 was a randomized trial in which patients ... had some degree of high-risk kidney cancer, either intermediate-high risk, high risk, or metastatic disease that was resected after surgery. Such patients who had surgery were then [randomly assigned] to receive either pembrolizumab or placebo for 1 year. The initial results had previously been reported and demonstrated a DFS [improvement] in this population, [which] led to the FDA approval of pembrolizumab for patients with high-risk kidney cancer after nephrectomy. [Pembrolizumab] has become a standard in many clinics for patients who have high-risk kidney cancer. After their surgery, they are receiving pembrolizumab for 1 year.

The primary analysis was done with 24 months of follow-up, and the updated analysis...
was done with 30 months of follow-up. What is important to note with the follow-up is that DFS was still strong, with a hazard ratio of 0.63. The 24-month DFS rate was 78.3% in patients receiving pembrolizumab and 67.3% in patients who were on the placebo arm, showing a nice risk reduction for patients receiving pembrolizumab and 67.3% in patients who received pembrolizumab vs placebo. The risk difference between the patients receiving pembrolizumab vs placebo was still strong, with a hazard ratio of 0.63. The 24-month DFS rate was 78.4% in patients receiving pembrolizumab vs 37.9% in patients who received placebo.

One of the interesting things reported were [the data for] the subgroups. For patients with intermediate-high risk, the benefit was about 9% in terms of the difference in recurrence between patients receiving pembrolizumab vs placebo. The risk difference between the patients receiving pembrolizumab and placebo was even greater in patients with higher risk and in patients with M1 no evidence of disease; in other words, patients who had some metastatic disease that was resected after surgery [TABLE].

One of the interesting things reported were [the data for] the subgroups. For patients with intermediate-high risk, the benefit was about 9% in terms of the difference in recurrence between patients receiving pembrolizumab vs placebo. The risk difference between the patients receiving pembrolizumab and placebo was even greater in patients with higher risk and in patients with M1 no evidence of disease; in other words, patients who had some metastatic disease that was resected after surgery [TABLE].

Another area of research is the duration of therapy. [It is important to keep] thinking about trial designs that take advantage of treatment-free intervals [and] thinking about the duration of therapy patients need to have that durable response.

These trials that have led to the remarkable results to benefit our patients. Much of the progress has been in treatment-naive metastatic RCC. Patients receiving their first line of therapy are now getting immune-based combinations, but what to do and how to manage those patients after their cancer progresses on frontline therapy remains a challenge.

Most of the agents that are available for refractory RCC have response rates of maybe 20% to 30% and a short progression-free survival, and at that point, patients tend to cycle from one therapy to the next. Is there some form of novel therapy? Is there some therapy that can produce a durable benefit in patients with refractory RCC? Those studies are ongoing.

These trials that have led to the remarkable results we see these days are predominantly in clear cell kidney cancer. Although clear cell RCC makes up 75% to 80% of all patients with RCC, that still leaves a lot of patients who do not have clear cell kidney cancer and need treatment options.

Another area of research is the duration of therapy. [It is important to keep] thinking about trial designs that take advantage of treatment-free intervals [and] thinking about the duration of therapy patients need to have that durable response.

What areas must still be addressed in future RCC research?

TiNivo-2 is investigating tivozanib, a highly selective VEGFR TKI, vs the combination of tivozanib with nivolumab. [This trial is] once again looking to answer that critical question of [whether there is] a role for immunotherapy-based treatment in patients whose kidney cancer has already progressed on immunotherapy.
FORGE AHEAD
WITH A BOLD APPROACH

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

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

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

IMPORTANT SAFETY INFORMATION

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

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

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

ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; RRMM=relapsed or refractory multiple myeloma.
 IMPORTANT SAFETY INFORMATION
 WARNINGS AND PRECAUTIONS

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

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 5% were in follow-up, and 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

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

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

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 35%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

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

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

Adverse Reactions

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.14 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (21%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 28% of patients. Adverse reactions resulting in a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
BLENREP
(belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

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

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

1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication is approved under accelerated approval based on response rate [see Clinical Studies (14.4) of full Prescribing Information] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms; 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 or 4 keratopathy (n = 149), 38% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

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

Monitoring and Patient Instruction

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

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

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

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

5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 15%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient.

Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 99). Among these patients, 22% were exposed for 6 months or longer.

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

Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratopathy</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>53</td>
<td>28</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Any Grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Calcium increased</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

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

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

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

| Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2 |
|--------------------------------|----------------|----------------|
| **Adverse Reactions**          | **BLENREP**    | **N = 95**     |
|                               | **All Grades (%)** | **Grade 3-4 (%)** |
| **Eye disorders**              |                 |                 |
| Keratopathy*                   | 71              | 44              |
| Decreased visual acuity*       | 53              | 28              |
| Blurred vision*                | 22              | 4               |
| Dry eyes*                      | 14              | 1               |
| **Gastrointestinal disorders** |                 |                 |
| Nausea                         | 24              | 0               |
| Constipation                   | 13              | 0               |
| Diarrhea                       | 13              | 1               |
| **General disorders and administration site conditions** |      |                 |
| Pyrexia                        | 22              | 3               |
| Fatigue*                       | 20              | 2               |
| **Procedural complications**   |                 |                 |
| Infusion-related reactions†    | 21              | 3               |
| **Musculoskeletal and connective tissue disorders** |   |                 |
| Arthralgia                     | 12              | 0               |
| Back pain                      | 11              | 2               |
| **Metabolic and nutritional disorders** | | |
| Decreased appetite             | 12              | 0               |
| **Infections**                 |                 |                 |
| Upper respiratory tract infection‡ | 11            | 0               |

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.
* Visual acuity changes were determined upon eye examination.
* Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
* Dry eyes included dry eye, ocular discomfort, and eye pruritus.
* Fatigue included fatigue and asthenia.
* Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthma, hypertension, lethargy, tachycardia.
* Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

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

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

**Gastrointestinal Disorders:** Vomiting.

**Infections:** Pneumonia.

**Investigations:** Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

| Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2 |
|--------------------------------|----------------|----------------|
| **Laboratory Abnormality**    | **BLENREP**    | **N = 95**     |
|                               | **All Grades (%)** | **Grades 3-4 (%)** |
| **Hematology**                |                 |                 |
| Platelets decreased           | 62              | 21              |
| Lymphocytes decreased         | 49              | 22              |
| Hemoglobin decreased          | 32              | 18              |
| Neutrophils decreased         | 28              | 9               |
| **Chemistry**                 |                 |                 |
| Aspartate aminotransferase increased | 57           | 2               |
| Albumin decreased             | 43              | 4               |
| Glucose increased             | 38              | 3               |
| Creatinine increased          | 28              | 5               |
| Alkaline phosphatase increased | 26             | 1               |
| Gamma-glutamyl transferase increased | 25          | 5               |
| Creatinine phosphokinase increased | 22         | 1               |
| Sodium decreased              | 21              | 2               |
| Potassium decreased           | 20              | 2               |

**6.2 Immunogenicity**

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

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

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

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

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

**Data**

**Animal Data:** Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

(continued on next page)
8.3 Females and Males of Reproductive Potential

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST). The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].

• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Alleviating the Burden of Financial Toxicity Begins at the Point of Care

by BRITTANY LOVELY

SAFETY PROFILES OF ANTICANCER drugs represent only one piece of the toxicity puzzle patients grapple with following a cancer diagnosis. Financial toxicity has come under the spotlight over the past 5 years as a topic that more clinicians are broaching not only with each other but with their patients.

“Financial toxicity has completely changed the way we view the patient, it’s changed the way we do business,” said Kathy Oubre, MS, chief executive officer of Pontchartrain Cancer Center in Covington, Louisiana, in an interview with OncologyLive®. “Oncology practices really have transformed over the past decade to treating the patient as a whole individual vs simply treating their disease.”

With nearly one-fourth of patients with cancer reporting treatment-related financial harm during their cancer journey, understanding determinants of financial toxicity at the point of care has become a pressing issue facing practices. “Cancer care has been expensive for a really long time, and it keeps getting more and more expensive,” said Amy Valley, PharmD, vice president of clinical strategy and technology solutions at Cardinal Health Specialty Solutions, in an interview with OncologyLive®. “But the good thing is that as an industry, there is a lot of focus on how we can ease the financial burden on patients with cancer.”

THE STARK REALITY OF CANCER COSTS

Valley noted that it is not uncommon for anticancer drugs to cost upward of $10,000 per month—and surgeries and other treatment expenses can send costs even higher. “The costs of care have [become] more expensive and insurance companies have pushed more of that cost down to the patients,” she said. “Imagine you are getting a really expensive therapy that your life depends on and there’s no alternative. The out-of-pocket costs, even for an individual who is insured, are not affordable and sustainable for many patients. It is...a really huge problem.”

For example, Valley pointed to an uptick in data tackling the burden of financial toxicity, such as the comprehensive report compiled by the National Cancer Institute. The report cites a 2012 survey indicating that among 4719 cancer survivors, 39.7% had made financial sacrifices to accommodate the costs of their cancer care and 33.1% had gone into debt, with 3.1% of respondents filing for bankruptcy.3

“The No. 1 cause of bankruptcy in the United States is medical bills,” Tanya Park, director of innovation solutions at Cardinal Health said. “If you think about how expensive cancer care is...some patients reach the breaking point financially. Individuals with a cancer diagnosis have just gone through this extraordinarily stressful clinical situation and now they have this additional financial stress...on top of it.” Park noted that patients with cancer who have declared bankruptcy are at an 80% higher risk of mortality.4

If patients are concerned about stretching their dollars, treatment adherence will begin to suffer and contribute to an increased mortality rate. “Prescription costs associated with cancer treatment play a role in treatment adherence,” Oubre said. “We know that [some] patients cannot afford their prescriptions, so they might cut their pills in half. They may miss doses in order to keep those pills longer.”

In a report on nonadherence, among 524 patients who reported financial toxicity, 17.7% needed but were unable to afford prescription medication compared with 3.4% of those who did not report financial toxicity (n = 1464).1 This translated to a relative risk of 3.55 (95% CI, 2.53-4.98).1

The challenges are not confined to therapeutic costs, hospitalization, and co-pays at practice visits. Transportation, lodging, reductions in employment hours, time off for appointments and procedures, as well as reduced efficiency are additional factors that feed into a patient’s comprehensive financial burden.3

“Although drug costs are certainly a driver of the increasing out-of-pocket cost for patients, these individuals are also getting a lot of different treatments,” Valley said. “Treatments may require them to be hospitalized, they can receive radiation therapy, they may have surgery, there are a lot of tests that are done for monitoring and ongoing observation...it’s a lifetime impact for these individuals in terms of the cost they incur.”

Widening the scope of care begins with the treating physician. Valley noted that throughout her career, there has been debate over whether it is up to the treating oncologist to have financial conversations with the patients at the point of care. “I think that physicians are now realizing financial conversations are a part of the informed decision-making process,” she said. “Providers need to be equipped with the information to have a conversation with patients about the financial aspects of the treatment options. That’s a big shift in medical care, and there’s still a gap in getting the information to the provider at the right time so they can have those conversations about treatment options.”

INTEGRATING SOLUTIONS IN PRACTICE

A gap in translating financial discussion into point-of-care decision-making is the lack of available data for oncologists. This includes gathering a comprehensive portrait of the patient and their unique social determinants of health in addition to the financial costs of care that
various adverse effects such as hospital and clinicians identify patients who are at risk for experience," Valley said. "Looking at the social and affect the financial hardship that patients experience, so many different aspects that can ultimately to paint the full patient picture. "There are factors affect outcomes, [treatment] adherence, and the whole cancer care journey for the patient and their families.”

In terms of tools available beyond intake, leveraging information already available to oncologists in electronic health records (EHRs) may provide a path forward. For example, Decision Path, developed by Cardinal Health’s innovation arm, Fuse, is built into the EHR workflow. It aims to provide estimates and comparisons by clinical indication and cost between different treatment regimens to enable clinicians to make optimal decisions at the point of care. "Decision Path is designed to be built into the EHR workflow, so that [the information is] right there at the point [a clinician] will be making a treatment decision," Park explained. “It’s designed to allow oncologists to compare different treatment options by clinical indications and risk and then provide them with a window into the cost of care as they’re making that decision.”

With the determinants that Oubre highlighted, Valley added that Decision Path coupled with value-based care platforms such as Cardinal Health’s Navista TS (Tech Solutions), can help to paint the full patient picture. “There are so many different aspects that can ultimately affect the financial hardship that patients experience,” Valley said. “Looking at the social and behavioral determinants of health can help clinicians identify patients who are at risk for various adverse effects such as hospital and emergency department visits, pain, and others, which are likely to influence outcomes and add to cost of care.”

Decision Path compares a variety of aspects of treatment regimen choices beyond financials, including clinical risk factors, and provides information on available biosimilar options. “Biosimilars are one way in which practices can address some of the increasing cost of drugs,” Park said. Decision Path will also provide oncologists with preloaded, practice-approved biosimilar substitutions allowing for cost-to-practice and cost-to-patient comparisons during the treatment decision process. “Biosimilars have really played a role in helping patients afford cancer treatments,” Oubre said. “It is important to keep in mind that by using these lower-cost products, we’ve seen an increase in access to care—more patients are able to afford treatments than before the advent of biosimilars.”

**SMALL BUT MONUMENTAL STEPS FORWARD**

Finally, Valley noted that although the data surrounding financial toxicity have been enlightening and long overdue, she is more excited that actions are being taken to address the issues. “That’s what I love most about the work I’m involved with…we’re designing tools to operationalize an action plan that helps individuals do something about financial toxicity and make a difference,” she said. “The past 5 years have been about measuring, quantifying, producing statistics, and selecting some of the low-hanging-fruit action plans. Now we are asking: how can we go to the next level? These tools are one of many things that I think are going to start really moving the needle on addressing financial toxicity.”

Although Valley notes that these tools are not a cure-all, presenting the information to clinicians in a way that facilitates early discussions and provides opportunities to address issues of financial burden upfront is “what’s really important to us.”

Oubre also expressed optimism at the future of care for her patients but noted that with change comes room to reflect on what is and is not working in daily practice. “When I first started [seeing patients], you just saw the patients deliberate their cancer treatments,” Oubre said. “It segmented the way we did business. Now we have a financial assistance team and we work very hard with our patients and their families to help them manage and afford their cancer treatments.”

“We’ve come a long way by embedding programs such as financial assistance, distress screening, and survivorship care. We always need to strive to do better by our patients and their families by stressing to our cancer care teams the importance of these programs and pulling them through [the process]. We need to walk the walk and make these programs part of what we live and breathe and do every day in practice.”

To learn more about Cardinal Health Navista TS, visit cardinalhealth.com/navista.

**REFERENCES**


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"**Financial toxicity** has completely **changed** the way we view the patient, it’s **changed** the way we do business. Oncology practices really have **transformed** over the past decade to treating the patient as a **whole individual** vs simply treating their disease.”

— KATHY OUBRE, MS
Struggles to Afford Care Continue for Medicare Patients

by TODD SHYROCK

FROM 2021 TO 2022, the monthly premium for Medicare Part B increased by 14.5%, the largest price hike in the program’s history. As a result, 60% of Medicare recipients predict they will have difficulty affording health care this year, according to a new survey by Medicare Plans.

Of those surveyed (n = 1250), 18% said affording health care expenses will be “very difficult” after the price increase, and 42% said it will be “somewhat difficult.” In addition, 20% of Medicare recipients indicated that they spend 50% or more of their monthly income on health care expenses. As a result, half will have to forgo some type of medical care in 2022. Specifically, the monthly premium rose from $148.50 to $170.10.

“Most years, we expect a Medicare price increase, but in 2021 that increase was limited by the CARES Act in response to the COVID-19 pandemic,” Kellie Blackwell, a senior adviser at Medicare Plans, said in a statement. “Now the Centers for Medicare & Medicaid Services is playing catch-up. The higher premium is expected to fund Medicare spending and [maintain] a reserve. Additionally, the uncertainty around Medicare coverage of some drugs, like the new Alzheimer drug Aduhelm [aducanumab-avwa], was another factor in the price increase.”

Medicare patients are having to make difficult decisions. The majority, 51%, are reducing discretionary spending on things such as travel and entertainment. However, 29% are also cutting back on necessities, including groceries and utility bills. Twenty-three percent of seniors are coping with inflation by dipping into savings, and 15% are trying to reduce their health care costs by skipping prescription medications or delaying medical procedures.

Twenty-one percent of respondents say it is “very likely” they will forgo medical care and 28% say it is “likely.” Seniors are most likely to skip medical care that is not covered by Medicare, including dental care (41%) and vision care (34%). Twenty-nine percent will skip routine check-ups, and 26% will forgo outpatient procedures.

Twenty-seven percent of those who anticipate difficulty paying for health care costs say they may have to come out of retirement and start working again. Further, 22% of those who have not retired yet say they will continue working, even though they are eligible for retirement. The majority of these respondents, 40%, will turn to savings to cover health care costs and other expenses. Sixteen percent will turn to children or other family members for financial assistance.

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Precursor Conditions Unlock Potential for Early Interventions in Multiple Myeloma

by SHONALI MIDHA, MD; OMAR NADEEM, MD; and IRENE GHOBRIAL, MD

**MULTIPLE MYELOMA ARISES FROM** precursor conditions, including monoclonal gammapathy of undetermined significance (MGUS) and smoldering myeloma. Since MGUS was first described more than 40 years ago, its definition and implications have continued to evolve. Data presented at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition underscored the growing focus on improving screening, advancing methods of detection, and improving our understanding of the genomic, genetic, and epigenetic factors that govern progression and therapeutic resistance.

No routine screening process is established for multiple myeloma or other blood cancers among the general population, despite the availability of a simple blood test with better sensitivity and specificity of detection for monoclonal protein than intrusive and potentially nonsensitive studies such as mammograms and colonoscopies. The argument for many years has been that early detection offers no benefit because of low rates of progression and unclear survival advantages. However, this argument is not valid with recent data that demonstrate early intercceptions have a significant beneficial effect on survival.

The prevalence of MGUS is approximately 3% to 5% among Americans older than 50 years. However, these statistics are based on a predominantly White population, use old technologies of serum protein electrophoresis, and do not account for at-risk individuals (based on race or family history). MGUS and multiple myeloma exhibit one of the largest racial disparities of all cancer types.

Compared with White Americans, Black Americans have a 2- to 3-fold higher MGUS prevalence. A growing body of evidence suggests that heritable factors may influence this racial disparity, with results of several studies demonstrating that a family history of multiple myeloma or a related autoimmune disorders. In addition, screening did not demonstrate an effect on survival because of cancer worry across the pre- and post-screening interval. These results indicate that older adults in these populations could benefit from regular, high-sensitivity screening to identify MGs and to consider further investigation into their risk for MM and other comorbidities.

**BEYOND SCREENING**

In addition to screening, another increased focus has been on improved, less-invasive methods of detection and surveillance in multiple myeloma. Minimal residual disease (MRD) assessments are a highly sensitive tool for assessing depth of response, risk stratification, and treatment of patients. Achieving MRD negativity is associated with improved progression-free survival (PFS), regardless of high-risk disease features.

Bone marrow–based MRD assessments are limited by their invasive nature, heterogeneity of marrow involvement, and cost of the available assays. Mass spectrometry (MS) is being evaluated by investigators as a more sensitive method of measuring paraproteinemia and has recently been approved by the International Myeloma Working Group (IMWG) for use that active screening identified a significantly higher number of individuals with any lymphoproliferative disorder, specifically smoldering Waldenström macroglobulinemia, smoldering myeloma, and multiple myeloma. Interestingly, of the 1279 patients randomized to intensive follow-up, bone marrow sampling from 970 participants revealed smoldering myeloma in 105 (10.8%) individuals. The prevalence of smoldering myeloma was 0.53% in the population of participants 40 years and older. Thus, the iStopMM study demonstrated the value of screening for early detection and intervention, although evidence of the effect on survival outcomes is yet to be determined.

**PROMISE STUDY**

Investigators of the PROMISE study only screened individuals in high-risk populations, namely Black Americans and those with a first- or second-degree relative with a blood cancer. The study population included 7600 screened patients using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) as well as serum protein electrophoresis and immunofixation. The overall prevalence of MGUS, as detected by MALDI-TOF MS, was 10%. Screening identified monoclonal gammapathies (MGs) in 40% of high-risk individuals 50 years and older, with 13% having high-concentration MGs (MS-MGUS); a lower-concentration fraction of MGs was further defined as monoclonal gammapathy of indeterminate potential (MGIP).

Significantly worse overall survival was reported among those with MGs and, more specifically, among those with MS-MGUS or high-MGIP. Moreover, MGs were associated with developing blood cancers, cardiovascular diseases, and autoimmune disorders. In addition, screening did not demonstrate a significant effect on health-related quality of life or anxiety because of cancer worry across the pre- and post-screening interval. These results indicate that older adults in these populations could benefit from regular, high-sensitivity screening to identify MGs and to consider further investigation into their risk for MM and other comorbidities.

**iStopMM CLINICAL TRIAL**

iStopMM is the first population-based, unbiased screening study for MGUS that includes a randomized trial component to assess follow-up strategies. All Icelandic residents born before 1976 (age ≥ 40 years) were eligible to participate, and blood samples were collected alongside blood sampling in the Icelandic health care system. A total of 75,422 participants provided a serum sample for screening, of which 3725 (4.9%) had MGUS.

MGUS prevalence was dependent on age, with 2.3%, 6.2%, and 12.9% of diagnoses occurring in age groups 40 to 59 years, 60 to 79 years, and 80 to 103 years, respectively. With a median follow-up of 3 years, data from the randomized control trial evaluating follow-up strategies revealed...
in lieu of immunofixation. Giles et al assessed the prognostic effect of detectable residual monoclonal free light chains by MALDI-TOF MS in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM). They found that MS positivity was associated with shorter PFS than MS negativity, regardless of response attained as defined by IMWG criteria. This held true in patients with MRD negativity on maintenance therapy, with results demonstrating that those who were MRD negative and MS positive had a shorter time to progression (TTP) than those who were MRD negative and MS negative. Thus, MS provides an alternative to invasive bone marrow testing and may provide additional sensitivity for residual disease detection and prognosis.

Similarly, evaluating circulating tumor cells (CTCs) by next-generation flow has been found to hold prognostic value. Garcés et al evaluated CTCs in patients with smoldering myeloma and NDMM, finding CTCs were detected in 248 of 316 (78%) patients with smoldering myeloma and in 597 of 650 (92%) patients with NDMM. Untreated patients with smoldering myeloma (n = 230) with high CTC levels (≥ .02%) exhibited ultrahigh risk of transformation vs those with low and undetectable CTCs (median TTP, 11 months vs not reached, respectively; P < .0001). An evaluation from Dutta et al of CTCs in patients with MGUS or smoldering myeloma corroborates these findings. The results demonstrated that higher CTC counts correlated with increased disease risk and that genomic profiling of CTCs was congruent with bone marrow multiple myeloma cell expression, capturing 100% of clinically annotated bone marrow fluorescence in situ hybridization (FISH) copy number variation (CNV) events as well as expanding yield by identifying CNVs and MYC rearrangements not observed by FISH. Notably, patients with smoldering myeloma and at least 0.02% CTCs enrolled in the GEM-CESAR trial (NCT02415413) have not reached a median TTP. Thus, early intervention abrogated the poor prognosis of high CTC levels.

The value of early treatment in precursor conditions has been shown previously, such as in the phase 2/3 ECOG trial of lenalidomide (Revlimid) vs observation in patients with intermediate-risk and high-risk smoldering myeloma, in which treatment significantly delays progression to symptomatic multiple myeloma and the development of end-organ damage without negatively affecting quality of life. With the goal of developing deeper remissions and potential for cure, several ongoing studies are evaluating the efficacy of combination therapies in MGUS and/or smoldering myeloma including the following:

- the B-PRISM study (NCT04775550) of daratumumab (Darzalex), bortezomib (Velcade), lenalidomide, and dexamethasone in patients with high-risk smoldering myeloma;
- a phase 2 trial (NCT02916771) of ixazomib (Ninlaro), lenalidomide and dexamethasone in high-risk smoldering myeloma;
- a phase 2 study (NCT03236428) of daratumumab in patients with high-risk MGUS and low-risk smoldering myeloma; and
- the GEM-CESAR trial of carfilzomib (Kyprolis), lenalidomide, and dexamethasone (KRd), induction, followed by autologous stem cell transplantation, KRd consolidation, and Rd maintenance in patients with high-risk smoldering myeloma.

Early findings have shown combination therapies employed in precursor settings are effective and well tolerated, with patients achieving high rates of deep, MRD-negative responses, and prevent progression to overt multiple myeloma. However, survival advantages remain to be seen.

### TABLE. Observations From the iStopMM and PROMISE Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Key findings</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMISE (NCT03689595): a study to determine clinical/genomic alterations present in individuals with MGUS and smoldering myeloma, who are diagnosed though screening of a high-risk US population.</td>
<td><strong>Key findings:</strong> a high prevalence MGUS was found among older Black adults and those who have a first-degree relative with a hematologic malignancy. These individuals may benefit from precision screening approaches to allow for early detection and clinical intervention.</td>
<td>For a full list of references, see the article at OncLive.</td>
</tr>
<tr>
<td>Interim screening data</td>
<td>Total screened (n = 2960)</td>
<td><strong>Interim screening data</strong></td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>59 (40-96)</td>
<td><strong>Race</strong></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td><strong>Black</strong></td>
<td>66%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>34%</td>
<td><strong>Age at screening 50-64 years</strong></td>
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<tr>
<td><strong>Age at screening ≥ 65 years</strong></td>
<td><strong>Interim screening data</strong></td>
<td><strong>Total screened (n = 70,444)</strong></td>
</tr>
<tr>
<td><strong>Individuals with MGUS</strong></td>
<td><strong>N = 3487</strong></td>
<td><strong>Prevalence</strong></td>
</tr>
<tr>
<td><strong>Risk stratification</strong></td>
<td><strong>Age 40-59 years</strong></td>
<td>2.3%</td>
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<tr>
<td></td>
<td><strong>Age 60-79 years</strong></td>
<td>6.2%</td>
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<td></td>
<td><strong>Age 80-103 years</strong></td>
<td>12.9%</td>
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</table>

MGIP, monoclonal gamopathy of indeterminate potential; MGUS, monoclonal gamopathy of undetermined significance.
died from a cerebrovascular event.

IMPORTANT SAFETY INFORMATION

• Non-metastatic castration-resistant prostate cancer (nmCRPC)

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

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

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

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® (see Use in Specific Populations (8.3, 8.4)).

ADVERSE REACTIONS

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (2.2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grades 3-4)

• Hematology — In the TITAN study: white blood cell decreased ERLEADA® 29% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.8%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)

• Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0.6%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (0.5%)

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

FRACTURES — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. The median time to first fracture was 33.5 months vs 16.2 months; HR=0.28; P<0.0001. In the TITAN study, conventional imaging (technetium-99m bone scans and computed tomography) was used to confirm that patients were non-metastatic at screening for this study. Patients with a history of seizure, predisposing factors for seizure, or receiving chemotherapy should be closely monitored for seizures. If seizures occur, ERLEADA® should be permanently discontinued.

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (2.2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

The following TITAN primary analysis results are included in the ERLEADA® Prescribing Information:

Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053.¹
START EARLY WITH ERLEADA®
TO PUSH BACK ON PROGRESSION

UPDATED RESULTS: OVERALL SURVIVAL FOR TITAN FINAL ANALYSIS

TITAN study*: therapy to achieve a 35% reduction in the risk of death in FDA-approved labeling for mCSPC
(ERLEADA® + ADT vs placebo + ADT; median OS: NR vs 52.0 months; HR=0.65; 95% CI: 0.53, 0.79)1,2

SPARTAN study*: AR inhibitor to improve median MFS by 2 YEARS in nmCSPC
(ERLEADA®+ ADT vs placebo + ADT; 40.5 months vs 16.2 months; HR=0.28; 95% CI: 0.23, 0.35; P<0.0001)1,2

SPARTAN study*: therapy to improve median OS by 14 MONTHS in nmCRPC
(ERLEADA® + ADT vs placebo + ADT; 73.9 months vs 59.9 months [5 years]; HR=0.78; 95% CI: 0.64, 0.96; P=0.0161)1,2

(1.0%); hypertriglyceridemia ERLEADA® 67% (1.6%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (1.9%), placebo 22% (0.5%)

Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rash (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).
The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP3A or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (See Dosage and Administration [2.2]).

Effect of ERLEADA® on Other Drugs

CYP3A4, CYP2C9, and UGT Substrates — ERLEADA® is a strong inducer of CYP3A4 and CYP2C9, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4 and CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucurononitransferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.
P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure to these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

ADT = androgen deprivation therapy; AR = androgen receptor; CI = confidence interval; CT = computed tomography; GBRH = gonadotropin-releasing hormone; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; MFS = non-metastatic survival; MFS = non-metastatic castration-resistant prostate cancer; NR = not reached; OS = overall survival; PSA = prostate-specific antigen; PRS = radiographic progression-free survival; SPARTAN = Selective Prostate Androgen Receptor Targeting with Apalutamide; TITAN = Targeted Investigational Treatment Analysis of Novel Androgens.

Study Design: TITAN was a phase 3, multinational, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1,152). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival and [HR=0.73; 7.1 patients enrolled in the TITAN trial started ADT for mCSPC 16 months prior to randomization].

Study Design: SPARTAN was a phase 3, multinational, randomized, double-blind, placebo-controlled trial of patients with nmCSPC (N=1,207). Patients had a PSA doubling time ≤10 months and serum testosterone levels ≤50 ng/mL. All patients enrolled were confirmed to be non-metastatic by blinded interim imaging review. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the pelvic bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastases, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of systemic chemotherapy.1,2

1 In the SPARTAN study, conventional imaging (the median-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph nodes ≤2 cm in short axis (N1) located below the pelvic bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastases, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of systemic chemotherapy.1,2


Visit erleadahcp.com

TITAN = Targeted Investigational Treatment Analysis of Novel Androgens.
Brief Summary of Prescribing Information for ERLEADA® (apalutamide) tablets

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

Cerebrovascular and Ischemic Cardiovascular Events

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

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from ischemic cerebrovascular events.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA and 1% of patients treated with placebo [see Adverse Reactions]. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

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

**Fractures**

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

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 2.7% of patients treated with ERLEADA and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

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

**Seizure**

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 460 days after initiation of therapy. There were no patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

**Embryo-Fetal Toxicity**

The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the last dose of ERLEADA [see Use in Specific Populations and Clinical Pharmacology (12.1) in Full Prescribing Information].

**ADVERSE REACTIONS**

The following are discussed in more detail in other sections of the labeling:
- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions]
- Fractures [see Warnings and Precautions]
- Falls [see Warnings and Precautions]
- Seizure [see Warnings and Precautions]

**Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most commonly reported adverse reaction (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and nausea.

**McKee Metastatic Castration-sensitive Prostate Cancer (mCSPC)**

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. In patients treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from ischemic cerebrovascular events.

Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardiac arrest (n=1), heart failure (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2.3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (≥1%) were rash, fatigue, hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

**Table 1: Adverse Reactions in TITAN (mCSPC)**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA (% of Patients)</th>
<th>Placebo (% of Patients)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
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<tr>
<td>Lymphocytes decreased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
<tr>
<td>Leukocytosis increased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
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<tr>
<td><strong>Hematology</strong></td>
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<tr>
<td><strong>Chemistry</strong></td>
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<tr>
<td>Hypercalcemia decreased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
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<tr>
<td><strong>Hypercalcemia</strong></td>
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<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td>50</td>
<td>20</td>
<td>+30</td>
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**Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference ≥ 5% All Grades) in TITAN (mCSPC)**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA (% of Patients)</th>
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<tr>
<td><strong>Hematology</strong></td>
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<tr>
<td>Lymphocytes decreased</td>
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<td>+30</td>
</tr>
<tr>
<td>Leukocytosis increased</td>
<td>50</td>
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<td>+30</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia decreased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
</tbody>
</table>

**Table 3: Adverse Reactions in SPARTAN (nmCRPC)**

A PARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone ( GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo. Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥ 2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=2). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3.2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 32% of patients. The most common (≥1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematia. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (≥2%) were fracture (3.4%) in the ERLEADA arm and urinary retention (3.8%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

**Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients at a Higher Incidence than Placebo (Between Arm Difference ≥ 5% All Grades) in SPARTAN (nmCRPC)**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA (% of Patients)</th>
<th>Placebo (% of Patients)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
<tr>
<td>Leukocytosis increased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia decreased</td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td>50</td>
<td>20</td>
<td>+30</td>
</tr>
</tbody>
</table>
**ERLEADA® (apalutamide) tablets**

### Most Common Adverse Reactions

- The most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA arm compared to the placebo arm include:
  - **Fatigue**
  - **Nausea**
  - **Vomiting**
  - **Hypertension**
  - **Hematuria**

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA include:

- **Fractures**
- **Seizure**
- **Falls**

For a complete list of adverse reactions, please see the Adverse Reactions section.

### Pregnancy

Adverse reactions that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to the placebo arm include:

- **Hot flush**
- **Arthralgia**
- **Hypercholesterolemia**
- **Hyperglycemia**
- **Hypertriglyceridemia**
- **Cancer**

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA include:

- **Peripheral edema**
- **Generalized edema**
- **Edema**
- **Penile edema**

### Lactation

Thyroid dysfunction was reported for 8% of patients treated with ERLEADA and 1.5% of patients treated with placebo. Grade 3-4 thyroid dysfunction occurred in 0.3% of patients treated with ERLEADA and 0.0% of patients treated with placebo.

Treatment decisions should be made considering the potential benefits of ERLEADA therapy and the risks of hypothyroidism.

### Contraindications

- **Hypersensitivity to the active substance (apalutamide) or any of its excipients**
- **History of unstable angina, myocardial infarction, congestive heart failure, stroke, or cerebrovascular event**

### Cautions

- **History of cerebrovascular event**
- **Hypothyroidism**
- **History of anaphylaxis or other severe reactions to drugs**

### Drug Interactions

- **P-gp, BCRP, or OATP1B1 Substrates**
- **Strong CYP2C8 or CYP3A4 Inhibitors**
- **Strong CYP2C19 Inhibitors**

### Animal Data

- **Teratogenic Effects**
  - Apalutamide is a weak inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans.

### Clinical Pharmacology

- **Elimination**
  - Apalutamide is eliminated primarily through the bile following hepatic metabolism.
- **Plasma Concentration**
  - The pharmacokinetics of apalutamide are not affected by food, and an orally administered dose of apalutamide is comparable to an equivalent intravenous dose.

### Pediatric Use

- **Safely and effectiveness of ERLEADA in pediatric patients have not been established.**

### Geriatric Use

- **Of the 1237 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 to 74 years, and 40% were 75 years and older.**
- **No overall differences in effectiveness were observed between older and younger patients.**

### OVERDOSAGE

- **There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.**

### Use in Specific Populations

- **Pregnancy**
  - Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy. Male fertility may not return to normal after treatment with ERLEADA.

### Dosage and Administration

- **Informed patients receiving concomitant gonadotropin-releasing hormone ( GnRH ) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.**
- **Instruct patients to take their dose at the same time each day ( once daily ). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.**
- **Instruct patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day.**
- **Patients who have difficulty swallowing tablets should be instructed to take the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets.**

### Embryo-Fetal Toxicity

- **Advise male patients that ERLEADA may be harmful to a developing fetus.**

### Lactation

- **Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA.**

### Use in Specific Populations

- **Pregnancy**
  - A dose of 100 mg/kg/day caused ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 8 times, respectively, the AUC in patients.

### Manufacturing

- **Manufactured by:** Manufactured for: Janssen Ortho LLC

### References

[1] 2019 Janssen Pharmaceutical Companies

### Table 4: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (n=1,350)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>Placebo</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
<td>64</td>
<td>0.5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
<td>29</td>
<td>0.0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1.8</td>
<td>21</td>
<td>1.9</td>
<td>21</td>
</tr>
</tbody>
</table>

### Investigations

- **Injury, poisoning and procedural complications**

### Additional Information

- **Includes appetite disorder, decreased appetite, early satiety, and hypophagia.**
- **Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema.**
MAURIE MARKMAN, MD, CAN pinpoint the exact moment when he knew medicine would be his path. Growing up in Los Angeles, California, Markman always looked up to Irving Rascon, MD, his primary care physician at Kaiser Permanente. Dr Rascon consistently gave Markman and his family the highest quality of care. From a very early age, Markman admired his doctor’s compassion and expertise and knew that he, too, wanted to go into the medical field. “He was just so dedicated and cared so much about my parents, my sisters, and me,” Markman said. “When people ask, ‘Why did you want to go into medicine?’ that was it. And if someone asks, ‘How long ago did you know you wanted to be a doctor?’ I say, ‘As long as I can remember.’”

Little did he know he would go on to lead practice-changing research and clinical trials on gynecologic cancer, especially ovarian, as well as become the president of medicine and science at Cancer Treatment Centers of America and editor-in-chief of OncologyLive®, which are 2 positions he still holds.

Although Markman wanted to be a doctor since he was young, the thought of specializing in oncology did not come until after he earned his bachelor’s degree in biology at the University of Southern California in Los Angeles. He was a medical student at New York University School of Medicine in New York City, and graduated in 1974. After graduating, he did an internship in internal medicine at NYC Health + Hospitals/ Bellevue—formally Bellevue Hospital Center, New York University Medical Center—which he now considers “one of the finest training programs in the world.”

However, cancer care delivered at Bellevue may not have always been that way—especially decades ago, when the world of oncology was not as refined and well understood as it currently is. “At that hospital, I obviously saw some superb care. But at that point, there were no oncologists as I would see them today. There was a very strong hematology program, but basically, in the oncology program, the people who were giving the chemotherapy were, in fact, ‘chemotherapists,’” Markman said. To Markman, it seemed as if the medical professionals were mainly concerned with just administering chemotherapy to patients with cancer.

During his time at Bellevue, he eventually became chief resident of internal medicine before moving onto the research world in
1978, when he was a clinical associate in the Immunology Branch at the National Cancer Institute in Bethesda, Maryland. However, during his time in the laboratory, he found himself wanting to be back at the bedside. “What I realized was that the laboratory was interesting, but I really missed direct patient care,” he said. “Then I took what I considered to be an extraordinary opportunity to be a fellow at [The] Johns Hopkins Hospital and worked with an incredible medical faculty at the wonderful institution.”

So with a passion to do better and the intellectual challenge and excitement of treating cancer, Markman was hooked. He had found his calling. “One of the reasons why I went into this is I love the challenge,” he said. “But the most important part that went into it then—and it doesn’t change today—is the opportunity to have a favorable impact on patients and their families. It could not have been more Griffithing than taking care of patients and their families, because it was not a matter of cure, [and] it was not a matter of how long the therapy would last. It was a matter of helping patients through this incredibly difficult journey.”

After 2 years at Johns Hopkins in Baltimore, Maryland, where he served as an assistant in oncology and medicine, Markman was recruited by John Mendelsohn, MD, a 2016 Giants of Cancer Care® winner, to go to the University of California San Diego (UCSD) School of Medicine. The job change was something that would further not only his career but also his personal life.

At UCSD, Markman met his wife, Tomes Suzanne, who was an administrator at the cancer center. Then when Mendelsohn moved to New York, New York, to be the chair of medicine at Memorial Sloan Kettering Cancer Center (MSK), he asked Markman to come along, although Markman joked that he was not so sure this recruitment was all about the medicine. “I tell everyone that he didn’t really want to work with me. He just wanted to work with my wife, who would eventually come back after having our first child,” Markman said.

Markman and his wife went on to have 4 children, Margaret, Jonathan, Timothy, and Elisabeth, who have gone on to make him a grandfather a few times over. Markman admits that having a family he adored sometimes made it difficult to balance his demanding career as a medical oncologist with his role as a family man—2 things he was extraordinarily passionate about. “My wife is a saint,” Markman said. “I’m very proud of my children, but it’s my wife who has made it possible. As you can imagine, I worked very hard. I worked a lot of hours. And we have 4 children. That work-life balance has been and always will be a challenge, because I wanted to spend time with my children and I was also committed to my profession and my patients,” he said.

After 7 years at MSK, Markman moved on to be chairman of the Department of Hematology/Oncology and director of the Tauskig Cancer Center at the Cleveland Clinic in Ohio. Although it was already a wonderful opportunity, Markman said, living in the Cleveland area also allowed him to spend more time with his children, without hours spent on travel to and from New York City, which he had to endure while working at MSK and living in northern New Jersey.

“An important reason for [moving and changing jobs] was [to raise my] children in Cleveland. [Getting] home to watch my kids’ soccer games and school activities was a lot easier in Cleveland,” Markman said.

In 2004, Markman and his family headed south after he accepted the position of vice president of clinical research and professor of medicine at The University of Texas MD Anderson Cancer Center in Houston. Markman would also become the chairman of the Department of Gynecologic Medical Oncology there.

He returned to the Northeast in 2010, this time to serve as vice president of patient oncology services and national director of medical oncology at Cancer Treatment Centers of America in Philadelphia, Pennsylvania. A year later, Markman became the senior vice president for clinical affairs before ultimately accepting his current position as president of medicine and science.

Throughout his career, Markman has led and taken part in research that has had major implications in the way ovarian cancer is treated and understood. Some would call him a genius for this, but Markman humbly refers to himself as an observer. “I’ve tried very hard to be that observer, meaning my experiences with patients could potentially lead to observations that might benefit future patients, which, of course, gets you into the realm of clinical research,” he said.

Markman also did some of the earliest work in maintenance therapy with paclitaxel, again, he mentioned, based on observations from treating his patients. Thanks to some of the early phase 2 trials examining weekly paclitaxel in platinum- and paclitaxel-resistant ovarian cancer, Markman is credited, along with others, with defining the concept of retreatment of ovarian cancer and platinum-free intervals.

Markman said he feels humble to be considered a pioneer in oncology. However, his hard work day in and day out boils down to 1 motivation: the patients. “It’s the smile on the face of the patient, the firm handshake I get from the patient’s spouse, the ‘thank you’—that’s what makes it all worthwhile,” Markman said.

With that patient focus in mind, Markman has advocated for a shift in the way ovarian cancer trials are conducted, especially in the era of precision medicine. He believes overall survival in phase 3 trials should not be the only factor in the FDA’s consideration for approval of a drug. After all, that’s what it is all about.

“The Giants of Cancer Care® award is wonderful. I’m incredibly happy and proud of this, but what matters is the impact that I have seen and that was expressed to me. It’s that feeling that I’ve done something of value for the patient that is not defined by me but defined by them,” Markman said. “What matters is the patient.”
SERDs, \textit{ESR1} Mutations Dominate Updates in ER-Positive Breast Cancer

by BRITTANY LOVELY

\textbf{EMERGING APPROACHES FOR} overcoming resistance to endocrine therapy in patients with estrogen receptor (ER)-positive breast cancer are showing promise, according to recent clinical trial findings. For example, the development of several novel selective estrogen receptor degraders (SERDs) have demonstrated an expanding role for this patient population in combination and as monotherapy. Unpacking the role of detection and early intervention against \textit{ESR1} mutations also has sparked progress in tailoring treatment regimens leveraging the genomic data.

In a recent \textit{OncLive The Talk™} video program, Sara A. Hurvitz, MD, led a panel of breast cancer experts—Aditya Bardia, MD, MPH; Patrick Neven, MD, PhD; and Kevin Kalinsky, MD, MS—in a review of key data from the 2021 San Antonio Breast Cancer Symposium (SABCS). The program featured updates from several trials including the following:

- \textbf{AMEERA-1 (NCT03284957)}: a phase 1/2 study of amcenestrant in postmenopausal patients with ER-positive advanced breast cancer;\footnote{Investigators presented a readout with updated data for amcenestrant, an oral SERD, in combination with the CDK4/6 inhibitor palbociclib. All patients in this particular study were endocrine resistant. Approximately [25\% of patients had prior chemotherapy in the advanced setting and approximately] one-third were getting frontline therapy. The big picture [takeaway is that amcenestrant was a well-tolerated agent. There were some [reports of] low-grade nausea and fatigue and some hot flashes that might have been attributed to the SERD.}

- \textbf{EMERALD (NCT03778931)}: a phase 3 study of elacestrant vs standard of care for patients with ER-positive, HER2-negative advanced breast cancer;\footnote{For more information on the trials and the outcomes, see \textit{TABLES 1-4}.}

- \textbf{First-in-human study (NCT04072952)}: a phase 1/2 trial of ARV-471 alone and in combination with palbociclib (Ibrance) in patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer;\footnote{The other thing that was notable in the abstract was a clearance of \textit{ESR1} mutations, which included Y537S, which is a mutation that regarding SERDs, a new class of medications to treat ER-positive breast cancer. The first poster I want to go through relates to the updated data from AMEERA-1 looking at amcenestrant.}

- \textbf{PADA-1 (NCT03079011)}: a phase 3 clinical utility trial evaluating clinical benefit outcomes for patients who switch from treatment with an aromatase inhibitor plus palbociclib to fulvestrant plus palbociclib following detection of rising \textit{ESR1} mutations.\footnote{The dose was 200 mg with the approved dose of palbociclib [125 mg once daily], and investigators saw an [objective response rate of 34.2\%] and clinical benefit rate of [73.5\%] \textit{[TABLE 1]}.}

\noindent \textbf{UPDATES FROM 2021 SABCS IN ER-POSITIVE BREAST CANCER}

<table>
<thead>
<tr>
<th>NAME</th>
<th>INSTITUTION</th>
</tr>
</thead>
</table>
| Hurvitz, MD | Associate Professor  
David Geffen School of Medicine at UCLA  
Medical Director, Jonsson Comprehensive Cancer Center  
Clinical Research Unit  
Codirector, Santa Monica-UCLA Outpatient Oncology Practices  
Director, Breast Cancer Clinical Trials Program  
UCLA  
Los Angeles, CA |
| Bardia, MD, MPH | Medical Oncologist  
Massachusetts General Hospital  
Boston, MA |
| Neven, MD, PhD | Full Professor, Gynecological Oncology  
KU Leuven  
Member  
LKI–KU Leuven Cancer Institute  
Leuven, Belgium |
| Kalinsky, MD, MS | Associate Professor  
Department of Hematology and Medical Oncology  
Emory University School of Medicine  
Louisa and Rand Glenn Family Chair in Breast Cancer Research  
Director, Glenn Family Breast Center  
Director, Breast Medical Oncology  
Winship Cancer Institute  
of Emory University  
Atlanta, GA |
[is] resistant to the only approved SERD, which is fulvestrant.

These are some interesting data that have implications including in their ongoing studies in the phase 3 setting, such as in AMEERA-5 [NCT04478266], which is a frontline study comparing an AI [aromatase inhibitor] plus a CDK4/6 inhibitor vs this oral SERD plus a CDK4/6 inhibitor, specifically the CDK4/6 inhibitor palbociclib. We’ll see what the activity is for that in the frontline setting.

We’re all eagerly awaiting randomized data from AMEERA-3 [NCT04059484], which was a study of amcenestrant in pretreated patients vs physician-choice hormonal therapy. [There is] more to come with this agent, including ongoing studies in the operable setting that are ongoing at this time.

**HURVITIZ**

Very interesting data. What do you think of that objective response rate in this setting? A [rate of approximately one-third] is generous, but as you said, a fair number of the patients were [receiving amcenestrant] in the frontline setting. Do you think that the clinical benefit rate and objective response rate you saw were promising enough to support enrollment of these trials?

**KALINSKY**

Yes, I think so. Sometimes when you have such a heterogeneous group and you have patients including those who are getting a SERD in the second line or the third line, those response rates are not as robust and the degree of clinical benefit is not quite the same. [The data are] hard to interpret when it’s such a heterogeneous population, but amcenestrant is certainly a well-tolerated agent.

Seeing this clinical benefit rate really does make it seem promising in terms of the responses. I think this is why these randomized data are going to be so important—they’ll be in a specific setting. Looking at the combination of palbociclib with this drug in a frontline setting in a randomized study, that’s what’s really going to tell the story. It is certainly interesting and worthy of further evaluation.

**HURVITIZ**

And speaking of randomized data, Dr Bardia, you presented some big data at SABCS on elacestrant from the EMERALD study. Can you please go through your data and share with us what that study ended up showing?

**BARDIA**

Yes, absolutely. The EMERALD trial was a randomized phase 3 clinical trial looking at a novel oral SERD, elacestrant, vs endocrine therapy of physician’s choice as second- or third-line therapy for patients with ER-positive metastatic breast cancer. In the frontline setting we tend to use endocrine therapy plus a CDK4/6 inhibitor. The trial answered the question what to do after that in the second-line and third-line settings.

Patients were required to have disease progression following frontline treatment with a CDK4/6 inhibitor plus endocrine therapy. Investigators randomized [patients] to elacestrant vs endocrine therapy or physician’s choice therapy, which could either be an AI or fulvestrant. The study had coprimary end points of progression-free survival [PFS] in all patients and PFS in patients with ESR1 mutations, [which] confer resistance to AI, but not necessarily SERDs.

More than 450 patients were enrolled and randomized 1:1 to either standard of care or oral elacestrant. In terms of the results, the study met both its primary end points in all patients as well as patients with ESR1 mutations.

Among all patients there was a reduced risk of disease progression or death [with elacestrant], or in other words improvement in PFS [HR, 0.697] in the overall population. In patients with ESR1 mutations, the signal was stronger with a hazard ratio of 0.55.

Looking at the curves, there was an interesting trend that was seen, which was that there was a sharp decline early on in both arms. You could see a separation in the curves. The initial decline was likely due to endocrine resistance because the trial was looking at 2 different endocrine options as monotherapy. Patients who had endocrine-resistant disease just had disease progression. But then you could see a separation in the curve suggesting that in the endocrine-sensitive population, a better endocrine therapy is likely going to work better.

We looked at landmark analysis at 6 months and 12 months to really capture this point. And at 6 months the PFS rate was much higher.

---

**TABLE 1. Antitumor Activity and Safety of Amcenestrant in AMEERA-1**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amcenestrant plus palbociclib (n = 34)*</th>
<th>Reference</th>
</tr>
</thead>
</table>
| ORR (90% CI) | 32.4% (19.3%-47.8%) | 2
| CBR (90% CI) | 73.5% (58.4%-85.4%) | 2
| Median follow-up | 14.8 months | 2
| Median PFS, months (90% CI) | 14.7 (11.0-22.3) | 2
| 12-month PFS rate (90% CI) | 59.4% (43.8%-72.0%) | 2

**TABLE 2. Outcomes With Elacestrant vs Fulvestrant in EMERALD**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elacestrant (n = 239)</th>
<th>Fulvestrant (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>2.79 (1.94-3.78)</td>
<td>1.94 (1.87-2.10)</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>34.3% (27.2%-41.5%)</td>
<td>20.4% (14.1%-26.7%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>22.3% (15.2%-29.4%)</td>
<td>9.4% (4.0%-14.8%)</td>
</tr>
</tbody>
</table>

**ESR1-mutant disease**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elacestrant (n = 115)</th>
<th>Fulvestrant (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.78 (2.17-7.26)</td>
<td>1.87 (1.84-2.10)</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>40.8% (30.1%-51.4%)</td>
<td>19.1% (14.1%-26.7%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>26.8% (16.2%-37.4%)</td>
<td>8.2% (1.3%-15.1%)</td>
</tr>
</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th>AE</th>
<th>Elacestrant (n = 237)</th>
<th>Fulvestrant (n = 229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>35.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.0%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14.3%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.9%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

AE, adverse effect; PFS, progression-free survival; SOC, standard of care.

---

**TABLE 3. Outcomes With Palbociclib vs Fulvestrant in EMERALD**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Palbociclib (n = 34)</th>
<th>Fulvestrant (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.78 (2.17-7.26)</td>
<td>1.87 (1.84-2.10)</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>40.8% (30.1%-51.4%)</td>
<td>19.1% (14.1%-26.7%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>26.8% (16.2%-37.4%)</td>
<td>8.2% (1.3%-15.1%)</td>
</tr>
</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th>AE</th>
<th>Palbociclib (n = 34)</th>
<th>Fulvestrant (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flush</td>
<td>10.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.9%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

AE, adverse effect; PFS, progression-free survival; SOC, standard of care.

---

**TABLE 4. Outcomes With Elacestrant vs Fulvestrant in AMEERA-3**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elacestrant (n = 115)</th>
<th>Fulvestrant (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.78 (2.17-7.26)</td>
<td>1.87 (1.84-2.10)</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>40.8% (30.1%-51.4%)</td>
<td>19.1% (14.1%-26.7%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>26.8% (16.2%-37.4%)</td>
<td>8.2% (1.3%-15.1%)</td>
</tr>
</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th>AE</th>
<th>Elacestrant (n = 239)</th>
<th>Fulvestrant (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>35.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.0%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14.3%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.9%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

AE, adverse effect; PFS, progression-free survival; SOC, standard of care.
with elacestrant than standard of care, and similarly at 12 months was much higher. At 12 months it was approximately 20% with elacestrant vs less than 10% with standard-of-care endocrine therapy.

In terms of adverse effects [AEs], the No.1 AE was nausea. It’s an oral pill, so nausea was seen with this medication. But other than that, hot flashes, arthralgias were pretty much similar. Finally, in terms of overall survival [OS], at interim analysis there was a trend in favor of elacestrant vs standard-of-care endocrine therapy. But these data are not mature. In approximately a year or so we’ll have mature data to do final OS analysis.

Dr Neven is a coauthor on the abstract and upcoming manuscript as well [and] our take was that this study provides the first proof of principle, scientific proof of principle that elacestrant might be superior to standard endocrine therapy. But if you are looking at single-agent endocrine therapy, the adjuvant setting would be the best setting to evaluate 2 endocrine therapies. But these data are not mature. In terms of adverse effects [AEs], the No.1 AE was nausea. It’s an oral pill, so nausea was seen with this medication. But other than that, hot flashes, arthralgias were pretty much similar. Finally, in terms of overall survival [OS], at interim analysis there was a trend in favor of elacestrant vs standard-of-care endocrine therapy. But these data are not mature. In approximately a year or so we’ll have mature data to do final OS analysis.

In the later-line setting, we probably still need combination therapy. Single-agent treatment is not enough to result in robust PFS outcomes. But if you are looking at single-agent endocrine therapy, the adjuvant setting would be the best setting to evaluate 2 endocrine monotherapy agents.

**HURVITZ**

Very important proof-of-principle, phase 3 data, the first phase 3 randomized data to support the use of one of these oral SERDs. At last count I think we have approximately 8 ER degraders and blockers that are in development. It’s great to finally have these data in spite of the fact that [they] really do underscore the poor prognosis associated with heavily pretreated disease. That PFS is quite short in both arms, but [it is] great to see that elacestrant was better.

I want to turn now to another novel agent that blocks or degrades the ER. Using PROTAC [protein degrader] technology, there was a study looking at ARV-471. Dr Neven, can you take us through that data and explain to us a little bit about how this agent works?

**NEVEN**

There was a poster [presented at 2021 SABCS] on this new compound, and for me it seems to be really an ER degrader, as you said. It’s a small molecule targeting the ER. It indeed belongs to the PROTACs or virtualizes targeting chimera technology; there was a study looking at ARV-471. Dr Neven, can you take us through that data and explain to us a little bit about how this agent works?

**HURVITZ**

Thank you so much for that great description, [and] I think it is notable in this heavily pretreated patient population.

The VERONICA study [NCT03584009] looking at venetoclax [Venclexa] with fulvestrant [in patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer who experienced disease recurrence or progression during or after a CDK4/6 inhibitor] only yielded a clinical benefit rate of approximately 14% [with fulvestrant and 11.8% with the combination].6 Although 40% [with ARV-471] doesn’t sound great, when you look at the post CDK4/6-inhibitor setting, it is sort of notable that this drug is associated with this early evidence of activity.

I want to move now to an earlier-line setting, because we know there are a number of mechanisms of resistance to disease to therapeutics developed for ER-positive metastatic breast cancer, one of these being the acquisition of ESRI mutations. The PADA-I study was designed to look at switching patients from AI with palbociclib to fulvestrant plus palbociclib if there was a detection in a rise in ESRI ctDNA [circulating tumor DNA] without evidence of progression.

A very interesting trial design. Dr Bardia, can you take us through this study design and the early data presented at SABCS regarding PADA-I?

**BARDIA**

PADA-I was an interesting trial. It is a hybrid first/second-line or 1.5-line [setting] because the trial essentially enrolled patients who were on first-line therapy with an AI plus CDK4/6 inhibitor. Investigators monitored ctDNA in these patients, and if a patient had a rise in ctDNA during the treatment with AI plus CDK4/6, they were randomized to continue the same treatment or make an early switch to a SERD or fulvestrant. Patients could continue palbociclib.

Essentially it was asking the question: If there’s a rise in ctDNA, which could be suggestive of eventually disease progression, would making an early switch to a different endocrine backbone result in better outcomes? It was an interesting proof-of-principle trial. The team enrolled more than 1000 patients—1017 to be exact.

Among the 1017 patients, 172 had a rise in ctDNA and were randomized to receive AI plus palbociclib vs fulvestrant plus palbociclib [Table 4]. You had to screen a large number of patients to identify this group. The group of patients who switched from the endocrine backbone to receive fulvestrant plus palbociclib had better outcomes. The median PFS was 11.9 months compared with 5.7 in patients who had continued the same regimen of AI plus palbociclib.

These data provided a scientific proof of principle that if you switch therapy based on ctDNA.

### TABLE 3. Top Takeaways From First-in-human Study of ARV-471

<table>
<thead>
<tr>
<th>Antitumor activity</th>
<th>ARV-471 (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR* (95% CI)</td>
<td>40% (25%-56%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety all dose levels 30 mg to 700 mg (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAE Grade 1/2 Grade 3</td>
</tr>
<tr>
<td>Any TRAE</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Increased AST</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AST, aspartate aminotransferase; CBR, clinical benefit rate; TRAE, treatment-related adverse effect.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TABLE 4. Top Takeaways From PADA-I Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR defined as rate of confirmed complete or partial response or stable disease of at least 24 weeks and excludes patients unable to complete 1 cycle of treatment for reasons other than progressive disease, toxicity, or death.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Outcome</th>
<th>CBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI plus CDK4/6 inhibitor</td>
<td>Fulvestrant plus palbociclib</td>
<td>40%</td>
</tr>
<tr>
<td>AI plus CDK4/6 inhibitor</td>
<td>Fulvestrant plus palbociclib</td>
<td>30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 5. Top Takeaways From MONARCH 1 Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR defined as rate of confirmed complete or partial response or stable disease of at least 24 weeks and excludes patients unable to complete 1 cycle of treatment for reasons other than progressive disease, toxicity, or death.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Outcome</th>
<th>CBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI plus fulvestrant</td>
<td>AI plus fulvestrant</td>
<td>40%</td>
</tr>
<tr>
<td>AI plus fulvestrant</td>
<td>AI plus fulvestrant</td>
<td>30%</td>
</tr>
</tbody>
</table>

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**HURVITZ**

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NOW ENROLLING: Clinical Trials for Lung Cancer with TIL Cell Therapy

Investigational

Ph 2 Clinical Trials
Multi-Center
Non-Randomized
Non-Placebo Controlled

LN-145 (TUMOR INFILTRATING LYMPHOCYTES; TIL) is an investigational, personalized immunotherapy derived from the patient’s own immune cells.

KEY ELIGIBILITY CRITERIA:

- Diagnosis of Metastatic Non-small Cell Lung Cancer
- Disease progression after 1 or more lines of prior therapy which may have been a checkpoint inhibitor
- PD-L1 positive or negative status
- Tumors with EGFR, ALK, ROS mutations acceptable
- ECOG PS 0 – 1 (Fully active or able to carry out light work or activity)
- At least one tumor that can be safely removed by surgery for TIL and a second measurable tumor for response assessment

If these key eligibility criteria are met, you may be eligible to participate in our clinical study program. There are additional eligibility criteria that must be met and can only be assessed by a study physician.

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and effectiveness of this study has not been determined.

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CALL CENTER 1-866-565-4410, select option 3
VISIT www.iovance.com/clinical/iov-lun-202
EMAIL clinical.inquiries@iovance.com

CLINICALTRIALS.GOV
Lung Trial: NCT04614103
Solid tumor trial NSCLC cohorts: NCT03645928

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levels, that could result at least in improvement in PFS. The criticism of the study has been that we don’t know whether this early switch would eventually affect overall survival. Additional follow-up is needed. But scientifically, these data provide a nice concept where you can monitor ctDNA and act on it to make a change in therapy.

**HURVITZ**

Interesting as well that they required a rise in **ESR1** mutations and not just the presence of detectable **ESR1** mutation. I think a lot of investigators are taking note of these data as they design other studies looking at the use of SERDs in this type of setting.

I thought that this was a really interesting investigator-initiated study. And I wanted to highlight that there’s an ongoing study, a randomized global study that’s looking at this question with **SERENA-6** [NCT01464934] with an oral SERD [camizestrant; AZD9893] for patients who have received an AI and a CDK4/6 inhibitor, in this case palbociclib or abemaciclib. If **ESR1** mutations are detected, patients are randomized to continue on that vs switching to camizestrant plus a CDK4/6 inhibitor. Investigators are including a second PFS population, as well, to look at the total duration of response. [This will let us] see how an oral SERD plays out in a larger study.

**HURVITZ**

That’s interesting [that] investigators are using detection of **ESR1** mutations in that setting and not the rise in it. It may be easier to enroll actually because you’re not waiting for a rise.

**NEVEN**

I think we could take it a step further. If you have a patient with a very long disease-free interval, luminal-A-like metastatic disease, why not give single-agent endocrine treatment and look for **ESR1** mutation and then add the CDK4/6 inhibitor?

**HURVITZ**

There are so many questions that are begged. Every time we see data [such as these] coming from an elegantly designed trial, they generate a number of new questions and new ways for us to design trials going forward. I love it.

**REFERENCES**


To watch more episodes from the 2021 SABCS edition of OncLive The Talk®, scan the QR codes or visit the links below.

**Updates in Key Clinical Trials for Breast Cancer**

The panel share insights on updates in key clinical trials and novel therapies in breast cancer presented at 2021 SABCS. The data span patient populations and include updates from:

- Updates from the TEXT (NCT00065703) and SOFT (NCT00066690) trials which evaluated adjuvant aromatase inhibitor exemestane (Aromasin) plus ovarian function suppression (OFS) vs tamoxifen plus OFS in premenopausal women with hormone receptor-positive early breast cancer;
- The first results from the phase 3 RUXPONDER trial (NCT01272037) of standard adjuvant endocrine therapy plus or minus chemotherapy in patients with 1 to 3 positive nodes, hormone receptor-positive and HER2-negative breast cancer with a recurrence score of less than 25; and
- Data from the CCTGMA-32 (NCT01101438), a phase 3 randomized double-blind placebo-controlled adjuvant trial of metformin vs placebo in early breast cancer; and
- An analysis of datopotamab deruxtecan in a subgroup analysis of the TROPION-PanTumor01 study (NCT03491385)

**WATCH NOW:**

bit.ly/3IXo40K

**Updates in CDK4/6 Inhibitors in Breast Cancer**

The panel discusses updates from 2021 San Antonio Breast Cancer Symposium (SABCS) on the use of CDK4/6 inhibitors in hormone receptor-positive/HER2-negative breast cancer. Key data include:

- Results of genomic profiling of PAM50-based intrinsic subtype across the MONALEESA studies;
- The final efficacy and safety data on ribociclib (Kisqali), everolimus, exemestane ([Aromasin]) triplet therapy after progression on a CDK4/6 inhibitor from the TRINITI-1 trial (NCT02732119); and
- Data from the biomarker program of the PENELope-B trial (NCT01864744) investigating postneoadjuvant palbociclib (Ibrance) on the molecular plasticity of luminal A breast cancer and response to CDK4/6 inhibition.

**WATCH NOW:**

bit.ly/3pUkygm

**TABLE 4. PADA-1 Design and Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median PFS, months (95% CI)</th>
<th>PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PADA-1 step 2 (n = 279): Patients with <strong>ESR1</strong> mutations randomized to continue standard therapy with AI or switch to fulvestrant plus palbociclib</strong></td>
<td><strong>Al plus palbociclib</strong></td>
<td><strong>Fulvestrant plus palbociclib</strong></td>
</tr>
<tr>
<td></td>
<td>(n = 84)</td>
<td>(n = 88)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Efficacy outcomes after randomization</strong></td>
<td><strong>Efficacy outcomes in optional crossover arm</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Median PFS, months (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Al plus palbociclib</strong></td>
<td><strong>Fulvestrant plus palbociclib</strong></td>
</tr>
<tr>
<td><strong>Tumor progression in Al plus palbociclib arm</strong></td>
<td>5.7 (3.9-7.5)</td>
<td>11.9 (9.1-13.6)</td>
</tr>
</tbody>
</table>
Targeted Combo Notches Rare Success in GBM

by ANITA T. SHAFFER

FOR MORE THAN 20 YEARS, investigators have tried numerous targeted therapy strategies against glioblastoma (GBM) that have fallen frustratingly short in establishing clinical benefit.¹ That changed in November 2021 when an international team of investigators reported encouraging response rates to a dual-targeted regimen in patients with recurrent or refractory malignant brain tumors with BRAF V600E mutations.²

The combination of dabrafenib (Tafinlar), a BRAF inhibitor, and trametinib (Mekinist), a MEK inhibitor, demonstrated an objective response rate (ORR) of 33% (95% CI, 20%–49%) in patients with BRAF V600E-mutant high-grade gliomas, many of whom had GBM, according to interim data from the phase 2 Rare Oncology Agnostic Research (ROAR) trial (NCT02034110) published in Lancet Oncology.³

The findings represent the first time a targeted therapy has shown efficacy against GBM in a clinical trial, according to lead study author Patrick Y. Wen, MD, director of the Center for Neuro-Oncology at Dana-Farber Cancer Institute and a professor of neurology at Harvard Medical School, both in Boston, Massachusetts. Wen said the activity observed in the study is an encouraging sign that other targeted therapies may be effective against GBM, an aggressive malignancy that is the most prevalent primary brain cancer in adults.⁴⁻⁵

The prospect of a targeted therapy regimen for a subset of patients with malignant brain tumors comes at a time when the molecular underpinnings of these diverse and challenging cancers are increasingly recognized. In 2021, the World Health Organization (WHO) published its sixth version of international standards for classifying tumors of the brain and spinal cord. Although histology and immunohistochemistry analyses remain central to tumor diagnosis, multiple molecular parameters have been incorporated into the WHO guidelines for more precise identification. A prominent example is the classification of adult diffuse glioma subtypes including GBM by the presence or absence of an IDH1/2 mutation.⁶

Molecular testing also is gaining ground in clinical decision-making for a spectrum of brain cancers. National Comprehensive Cancer Network (NCCN) guidelines recommend integrated histopathological and molecular profiling for all gliomas, with data for a menu of molecular alterations considered noteworthy in a pathology workup (FIGURE).⁷

CLINICAL TRIAL FAILURES
Although investigators have explored many novel options, the frontline standard of care for GBM treatment remains surgical resection followed by radiotherapy and temozolomide. For recurrent disease, NCCN guidelines include protocols involving cytotoxic drugs, bevacizumab (Avastin), and regorafenib (Stivarga).⁸

The FDA has approved bevacizumab, a VEGF inhibitor, for recurrent glioblastoma based on progression-free survival (PFS) and response data.⁹ Regorafenib, which inhibits VEGF receptors and other kinases, demonstrated a benefit in median overall survival (OS) compared with lomustine (7.4 months vs 5.6 months; HR, 0.50; 95% CI, 0.33–0.75; P = .0009) in the phase 2 REGOMA trial (NCT02926222). However, the response rate with lomustine was lower than in other clinical trials, prompting some experts to question whether the study provides sufficient evidence of its efficacy against GBM.¹⁰

Overall, drug development efforts to expand FDA-approved treatment options with targeted agents have not succeeded despite a plethora of clinical trials. During a 20-year period ending in April 2020, there were 257 phase 1/2 through phase 3 studies that tested targeted regimens, according to an in-depth analysis by French investigators. Most of these studies (70%) were phase 2 trials. Only 12 of 37 studies with comparative data showed an improvement with a novel therapy, mostly in PFS.¹¹

Cruz Da Silva et al cited 3 key factors that contribute to targeted therapy failures against GBM: (1) the impossibility of performing a full surgical resection, (2) difficulty designing drugs that cross the blood-brain barrier, and (3) intratumoral molecular heterogeneity. Additionally, GBM is a comparatively rare cancer and clinical trial enrollment remains too low.¹²

Nevertheless, investigators continue to pursue targeted agents against GBM and other gliomas, with multikinase inhibitors and multitargeted regimens among the key trends.¹ Three ongoing clinical trials include studies evaluating various pathway inhibitors as well as targeted vaccines and combinations with immunotherapy. Several research teams also are using molecularly selected populations in basket studies to test multiple targeted agents (TABLE 1).

DABRAFENIB PLUS TRAMETINIB STUDY
In ROAR, US-based investigators joined with researchers from community and academic centers in 12 countries to study the combination of dabrafenib (150 mg twice daily) plus trametinib (2 mg daily) in 9 cohorts of patients with rare advanced BRAF V600E-mutated cancers. There were 2 cohorts for patients with gliomas (low-grade and high-grade tumors) as well as arms for anaplastic thyroid cancer, biliary tract cancer, gastrointestinal stromal tumor, hairy cell leukemia, multiple myeloma, and adenocarcinoma of the small intestine. Investigators also planned a cohort for patients with germ cell tumors but no one enrolled. In all, 206 patients 18 years and older enrolled from April 2014 through July 2018.¹³

The rationale for testing the targeted therapy combination against BRAF V600E-mutated gliomas stemmed from prior clinical data showing...
antitumor activity with single-agent BRAF inhibition in pediatric and adult patients with that tumor type. Investigators noted that dual blockade of MAPK pathway signaling with BRAF and MEK inhibitors has become a standard of care in BRAF V600-mutant melanoma, non-small cell lung cancer, and anaplastic thyroid cancer (TABLE 2).2
Understanding of the role of BRAF alterations also is growing across several brain cancer subtypes. BRAF V600 mutations that activate the MAPK pathway have been detected in 5% to 15% of low-grade gliomas but are less common in high-grade gliomas, including GBM, where they have been identified in approximately 3% of tumors.2 In the ROAR trial, investigators recruited 45 patients with recurrent high-grade glioma

### TABLE 1. Select Clinical Trials of Targeted Therapies in Adult Brain Cancers

<table>
<thead>
<tr>
<th>Novel agent (sponsor)</th>
<th>Study description*</th>
<th>Target enrollment</th>
<th>Phase (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct IDH-targeting therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorosidinib (AG-881 Institut de Recherches Internationales Servier)</td>
<td>Vorosidinib (IDH1/2 inhibitor) vs placebo in patients (&gt;12 years) with residual or recurrent grade 2 glioma with an IDH1 or IDH2 mutation</td>
<td>340</td>
<td>Phase 3 (NCT04164901)*</td>
</tr>
<tr>
<td>Olutasidinib (FT-2102 Forma Therapeutics, Inc)</td>
<td>Olutasidinib (IDH1 inhibitor) as a single agent and in combination with azacitidine in patients with IDH1 R132-mutant gliomas and GBM. (Trial includes additional cohorts and combinations for other solid tumors)</td>
<td>200</td>
<td>Phase 1/2 (NCT03848811)*</td>
</tr>
<tr>
<td>IDH305 (Novartis)</td>
<td>IDH305 (IDH1 R132 inhibitor) monotherapy in patients with IDH1 R132–mutant advanced malignancies including GBM</td>
<td>166</td>
<td>Phase 1 (NCT02381886)*</td>
</tr>
<tr>
<td>IDH1R132H peptide vaccine (German Cancer Research Center)</td>
<td>Monotherapy with vaccine or avelumab (PD-L1 inhibitor) or combination of vaccine plus avelumab in recurrent IDH1 R132H–mutated gliomas (WHO grade 2,3, or 4)</td>
<td>60</td>
<td>Phase 1 AMPLIFY-NEOVAC (NCT03893903)</td>
</tr>
<tr>
<td>BAY1436032 (Bayer)</td>
<td>Single-agent BAY1436032 (IDH1 inhibitor) in patients with IDH1 R132X–mutant advanced solid tumors, including GBM and anaplastic gliomas</td>
<td>81</td>
<td>Phase 1 (NCT02746801)*</td>
</tr>
<tr>
<td>LY3410738 (Eli Lilly and Company)</td>
<td>Single-agent LY3410738 (IDH1 R132 inhibitor) in patients with IDH1 R132–mutant advanced solid tumors, including gliomas</td>
<td>180</td>
<td>Phase 1 (NCT04521686)</td>
</tr>
<tr>
<td><strong>PARP inhibitors</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Olaparib (National Cancer Institute)</td>
<td>Olaparib monotherapy in patients with IDH1/2–mutant advanced solid tumors including GBM and other gliomas</td>
<td>145</td>
<td>Phase 2 (NCT03212274)</td>
</tr>
<tr>
<td>BGB-290 (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins)</td>
<td>BGB-290 plus temozolomide in patients with IDH1/2–mutant WHO grade 2-4 recurrent glioma</td>
<td>100</td>
<td>Phase 1/2 (NCT03914742)</td>
</tr>
<tr>
<td><strong>PKCβ, P38, AKT inhibitor</strong></td>
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<tr>
<td>Enzastaurin (DB102 Denovo Biopharma LLC)</td>
<td>Enzastaurin or placebo plus RT and temozolomide in newly diagnosed DGM1-positive GBM</td>
<td>300</td>
<td>Phase 3 ENGAGE (NCT03776071)</td>
</tr>
<tr>
<td><strong>MAPK pathway inhibitors</strong></td>
<td></td>
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<tr>
<td>Binimetinib plus encorafenib (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins)</td>
<td>Binimetinib (MEK1/2 inhibitor) plus encorafenib (RAF inhibitor) in patients with recurrent BRAF V600E/K–mutated GBM and other high-grade gliomas and PFA</td>
<td>62</td>
<td>Phase 2 (NCT03973918)</td>
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<tr>
<td><strong>MET pathway</strong></td>
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<tr>
<td>APL-101 (Apollomics Inc)</td>
<td>APL-101 (MET inhibitor) in patients with advanced solid tumors with MET aberrations, including GBM and other brain cancers with MET fusions or amplification</td>
<td>201</td>
<td>Phase 1/2 SPARTA (NCT03752224)</td>
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<tr>
<td><strong>Multikinase inhibitor</strong></td>
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<tr>
<td>Regorafenib* (Bayer)</td>
<td>Regorafenib plus nivolumab (PD-1 inhibitor) in recurrent or metastatic solid tumors including GBM (WHO grade 4) and anaplastic astrocytoma (WHO grade 3)</td>
<td>200</td>
<td>Phase 2 (NCT04704154)</td>
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<tr>
<td><strong>Platform/basket studies</strong></td>
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<tr>
<td>Multiple agents (Global Coalition for Adaptive Research)</td>
<td>Adaptive platform study testing regorafenib (multikinase inhibitor), palbociclib (PI3K inhibitor), or VAL-083 (alkylating agent) after RT plus temozolomide in newly diagnosed GBM or as monotherapy in recurrent GBM; control arm: RT plus temozolomide (newly diagnosed), temozolomide (recurrent)</td>
<td>1030</td>
<td>Phase 2/3 GBM AGILE (NCT03970447)</td>
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<tr>
<td>Multiple agents (Dana-Farber Cancer Institute)</td>
<td>Adaptive platform study testing temozolomide alone or with CC-115 (DNA-PK, mTOR inhibitor), abemaciclib (CDK4/6 inhibitor), or neratinib (HER2, EGFR inhibitor) in newly diagnosed MGMT-unmethylated GBM</td>
<td>250</td>
<td>Phase 2 INSIGHT (NCT02977780)*</td>
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<tr>
<td>Multiple agents (University Hospital Heidelberg)</td>
<td>Moleculary matched therapies plus RT in patients with newly diagnosed adult GBM without MGMT promoter methylation: APG-101 (CDK9 inhibitor); alecinita (ALK inhibitor); idasanutlin (MM2 antagonist); atezolizumab (PD-L1 inhibitor); vismodegib (Hedgehog inhibitor); palbociclib (CDK4/6 inhibitor); temsirolimus (mTOR inhibitor)</td>
<td>350</td>
<td>Phase 2/3 NCT Neuro Master Match-—NM2 (NCT03158389)</td>
</tr>
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</table>

DGM1, Denovo genomic marker 1; GBM, glioblastoma multiforme; PFA, anaplastic pleomorphic xanthoastrocytoma; RT, radiation therapy; WHO, World Health Organization.


*Trial is active but not recruiting participants.

*Regorafenib is a small-molecule inhibitor of VEGF receptors and other kinases.
Clinical Research Study: KN-8701 (NCT04913285)
Now enrolling patients with Class I, Class II, or Class III BRAF-mutated solid tumors and NRAS-mutated melanoma

Study Synopsis
KN-8701 is a multi-center, open-label, two-part clinical trial sponsored by Kinnate Biopharma to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of the small molecule pan-RAF inhibitor KIN-2787 in adults (18+) with Class I, Class II, or Class III BRAF-mutated advanced or metastatic solid tumors and NRAS-mutated melanoma.

The dose escalation portion (Part A) of the trial will determine the recommended dose and schedule of KIN-2787 for further evaluation in patients with BRAF mutation-positive solid tumors and NRAS mutation-positive melanoma.

The dose expansion portion (Part B) will assess the safety and efficacy of KIN-2787 at the recommended dose and schedule in patients with cancers that contain BRAF Class II or Class III mutations, including lung cancer, melanoma, and other selected solid tumors.

The U.S. Food and Drug Administration (FDA) cleared the Investigational New Drug application for KIN-2787 in May 2021 and the trial commenced on August 4, 2021. More information can be found at: ClinicalTrials.gov/ct2/show/NCT04913285.

Current Study Locations
- City of Hope, Duarte, California
- UCSD Moores Cancer Center, La Jolla, California
- Sarah Cannon Research Institute Lake Nona, Orlando, Florida
- Sarah Cannon Research Institute, Nashville, Tennessee
- Virginia Cancer Specialists, Fairfax, Virginia
- More study sites will be added
classified as WHO grades 3 or 4 by 2007 criteria and 13 participants with low-grade glioma of WHO grade 1 or 2. The primary end point was investigator-assessed ORR using Response Assessment in Neuro-Oncology (RANO) criteria. BRAF V600E mutation status was confirmed on tumor tissue, with a range of testing methods permitted.

In the high-grade cohort, the average age of patients was 53 years (range, 18-72). Most patients had undergone resection or craniotomy (93%) and were previously treated with chemotherapy (93%) and/or radiation therapy (RT; 98%) regimens. The most prevalent histologies were GBM in 31 patients (69%), followed by anaplastic pleomorphic xanthoastrocytoma and anaplastic astrocytoma, with 5 patients each (11% each). Among patients with low-grade gliomas, there were 9 responses, including 1 CR, 6 PRs, and 2 minor responses, for an ORR of 69% (95% CI, 50%-93%). Among the 31 patients with low-grade gliomas, anaplastic pleomorphic xanthoastrocytoma was diagnosed in 13 patients (42% each), 2 with CRs and 8 with PRs, for an ORR of 33% (95% CI, 20%-49%). Among the 15 patients in the high-grade cohort, 12 patients were evaluable for efficacy with 2 minor responses, for an ORR of 18.2% (95% CI, 5.2-40.3). An additional 16 patients (56.7%) had stable disease. With 59% of events reported, the median PFS was 36.8 months (95% CI, 11.2-90.4) for patients with nonenhancing glioma and 13.7 months (95% CI, 8.4-25.6) in the low-grade group, the median was not reached (NR) for PFS (95% CI, 7.4-NR) and ORR (95% CI, 11.6-NR).2

Moreover, the safety profile for the combination was consistent with clinical experience in other indications, investigators noted. Adverse events of grade 3 or worse severity were observed in 33% of patients, with fatigue (9%), decreased neutrophil count (9%), and headache and neutropenia (3% each) as the most frequently reported.

Outcomes in ROAR compare favorably with those for patients with recurrent high-grade gliomas in molecularly unselected populations treated with chemotherapy, investigators noted. “Response rates with chemotherapy have rarely exceeded 5%, with overall survival of 5 to 9 months and 3 to 4 months for glioblastoma after failing temozolomide and bevacizumab treatment,” they wrote. “In general, the progression-free survival for various salvage therapies in high-grade glioma was less than 3 months.”

Patients with low-grade gliomas who progress after chemotherapy also need new therapeutic options, investigators said, noting the added risk of transformation into a high-grade disease over time.

Moving forward, investigators suggested that the combination regimen be tested in a randomized clinical trial in treatment-naïve and previously treated patients with BRAF V600E-mutated high-grade or low-grade gliomas. Additionally, they recommended that BRAF V600E mutation testing be incorporated into molecular screening strategies.2

**ROLE OF IDH MUTATIONS**

Although mutations in several genes have been implicated in primary central nervous system tumors, mutations in IDH2 genes, which cause epigenetic modifications, have emerged as an important marker for adult-type diffuse gliomas.3-5 In the WHO standards, the presence of an IDH mutation frequently distinguishes lower-grade gliomas (WHO grades 2 and 3) whereas the absence of the aberration helps identify GBM.6 Somatic mutations in IDH1, most frequently at codon R132 (IDH1-R132H), have been detected in more than 70% of astrocytomas, oligodendrogliomas, and GBM that developed from the lower-grade lesions. IDH2 mutations were detected in 3.5% of these tumors. In adult primary GBM samples, 6% had IDH1 mutations and none had IDH2 mutations.5

Of note, the presence of IDH1/2 mutations has been strongly associated with more favorable outcomes, including OS, in grade 2 and grade 3 gliomas.7

Despite the significance of IDH1/2 mutations, however, there are no FDA-approved IDH inhibitors for brain cancer. Ivosidenib (Tibsovo), an IDH1 inhibitor, is indicated for IDH1-mutant acute myeloid leukemia (AML) in newly diagnosed patients who are 75 years or older or have comorbidities that preclude intensive chemotherapy and for patients with relapsed AML, as well as for patients with previously treated IDH1-mutant locally advanced or metastatic cholangiocarcinoma.8 Enasidenib (Idhifa), an IDH2 inhibitor, is approved for treating adults with IDH2-mutant relapsed or refractory AML.9 Both drugs have shown low brain penetration in preclinical studies, and investigators have turned their attention to novel agents for direct inhibition of IDH in gliomas.10 Among the most advanced novel agents in clinical development is vorasidenib (AG-821), a first-in-class dual inhibitor of IDH1 and IDH2 that was designed for improved penetration across the blood-brain barrier.11

In a first-in-human study (NCT02481154), vorasidenib monotherapy elicited responses in patients with IDH1/2-mutant lower-grade gliomas (WHO grade 2 or 3). The cohort included 22 patients with nonenhancing glioma, defined as the absence of enhancement on MRI, and 30 participants with enhancing glioma. Forty-one patients with a variety of other solid tumors also were enrolled but recruitment was halted to focus development on glioma.12

Among patients with nonenhancing gliomas, there was 1 PR and 3 minor responses by RANO criteria for an ORR of 18.2% (95% CI, 5.2-40.3). An additional 16 patients (72.7%) had stable disease. None of the participants with enhancing glioma showed a response, although 17 patients (56.7%) had stable disease. With 59% of events reported, the median PFS was 36.8 months (95% CI, 11.2-40.8) for patients with nonenhancing glioma and 3.6 months (95% CI, 1.8-6.5) for participants with enhancing glioma.13 Vorasidenib is being compared with placebo in the randomized phase 3 INDIGO trial (NCT04164901) in patients with WHO grade 2 oligodendroglioma or astrocytoma with an IDH1 or IDH2 mutation that has recurred after surgery. The study, which is open to patients 12 years and older, has an estimated primary completion date of October 2024.14

**TABLE 2. FDA-Approved BRAF/MEK Inhibitor Combinations**

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Indication with mutation (year of FDA approval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib + trametinib</td>
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<tr>
<td>Non–small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td>Dabrafenib + trametinib</td>
<td>Advanced or metastatic BRAF V600E-positive (2017)</td>
</tr>
<tr>
<td>Anaplastic thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Dabrafenib + trametinib</td>
<td>Metastatic/unresectable BRAF V600E-positive (2018)</td>
</tr>
</tbody>
</table>


For a full list of references, see the article at OneLive.com

82 Vol. 23 | No. 6 | MARCH 2022
Experts Survey Treatment Variations for Resectable NSCLC in Asian Populations

by CHRISTINA T. LOGUIDICE

SINCE THE DISCOVERY OF EGFR driver mutations nearly 2 decades ago, the scope of treatment for patients with non–small cell lung cancer (NSCLC) has undergone a revolution.1 These mutations are frequent in many Asian populations with NSCLC, observed in 47% to 64% of East Asian patients and in 22% of South Asian patients (ie, India) vs 10% to 20% of White patients,1,2 making them an especially important consideration across East Asia.

The emergences of several EGFR-targeted therapies have improved outcomes for patients. However, approvals for these agents vary across regions.

During an OncLive Peer Exchange®, a panel of lung cancer experts from China, South Korea, and Japan shared their insights on how they care for their patients with resectable EGFR-positive NSCLC.

They examined how treatment strategies differ between countries, including treatment of stage IB disease, use of postoperative therapy in stage III disease, and the use of EGFR tyrosine kinase inhibitors (TKIs) in the adjuvant setting. They also discussed the role of molecular testing in postoperative NSCLC, when to involve multidisciplinary care teams, and the diverging use of neoadjuvant therapy.

ADJUVANT TREATMENT STRATEGIES FOR RESECTABLE NSCLC

To reduce the risk of recurrence and metastasis, postoperative adjuvant treatment is recommended for patients with stage IIB to IIIA disease or partly stage IB and IIA disease with NSCLC who have undergone radical surgical resection.3 “For [patients with] resectable lung cancer, the guidelines indicate that for stage II and stage III [disease], the standard of care is adjuvant chemotherapy,” Yi-Long Wu, MD, PhD, said, adding that in China, this recommendation also extends to patients with high-risk stage IB disease. However, he noted that he does not use adjuvant chemotherapy for these patients. He said that in China, adjuvant use of gefitinib (Iressa) or osimertinib (Tagrisso) instead of chemotherapy has been approved for patients with EGFR-positive resected stage II to IIIA disease (N1-N2) based on data from the ADJUVANT/CTONG1104 (NCT01405079) and AURA1 trials, respectively.4,5

Shun Lu, MD, PhD, who also practices in China, said his institution follows a similar practice as Wu’s, but noted that adjuvant chemotherapy is sometimes recommended for high-risk patients with stage IB disease. He also noted that the icotinib, a first-generation TKI, is available to treat patients with stage II to III EGFR-mutant NSCLC.

In South Korea, the adjuvant chemotherapy recommendations mirror China’s. “All patients who have [had their disease] resected, from stage IB to IIA, should receive adjuvant chemotherapy first line as long as they have good performance status,” Myung-Ju Ahn, MD, said. When considering patients with stage IB disease, her
Postoperative Radiotherapy in Stage III NSCLC

The panelists agreed that postoperative radiotherapy is best reserved for patients with incomplete or uncertain resections, rather than the general population of patients with resectable stage III NSCLC. This consensus was partially based on findings from the LUNG ART study (NCT00410683), a phase 3 European randomized trial evaluating modern postoperative conformal radiotherapy (PORT) in patients with completely resected NSCLC and mediastinal N2 involvement.2 Results showed no overall survival (OS) benefit with the addition of PORT, although there was a nonstatistically significant 15% increase in disease-free survival (DFS) among patients with stage III (N2) disease.

“If the surgeon thinks the patient has a high possibility of local recurrence when they do surgery, then we give radiation. Other than that, we don’t routinely use postoperative radiation [in South Korea],” Ahn said. Wu agreed and said that in China, PORT is used only when resection is uncertain or incomplete, noting that data from a Chinese radiotherapy trial showed similar findings to LUNG ART. “There was no OS benefit from the postradiotherapy for N2 [disease] data,” he said.

Similarly, Mitsudomi said postoperative radiation is almost never used for N2 disease in Japan. He noted that this was the case even before the LUNG ART study data became available and said that the Japan Society of Clinical Oncology is currently conducting its own radiation study.

Using EGFR TKIs in the Adjuvant Setting

The role of EGFR TKIs in the NSCLC setting continues to evolve, with the third-generation agent, osimertinib, generating considerable excitement among the panelists. Osimertinib showed benefit as an adjuvant treatment for patients with EGFR-positive resectable NSCLC in the double-blind, phase 3 ADAURA trial.5 ADAURA randomly assigned 682 patients with completely resected EGFR-positive NSCLC 1:1 to receive adjuvant osimertinib 80 mg once daily (n = 339) or matching placebo (n = 343) for 3 years.5 The primary end point was DFS among patients with stage II to IIIA disease. Secondary end points included DFS in the overall study population (stage IB to IIIA disease), OS, and safety. Adjuvant platinum-based chemotherapy was allowed and was administered to 76% of patients with stage II to IIIA disease (n = 466) and 26% of patients with stage IB disease (n = 216).5

Among the patients with stage II to IIIA disease, 90% of the patients in the osimertinib arm were alive and disease free at 24-month follow-up compared with 44% of those in the placebo arm (HR for disease recurrence or death, 0.17; 99.06% CI, 0.11-0.26; P < .001). When examining the entire study population, 89% of the patients in the osimertinib arm and 52% of patients in the placebo arm were alive and disease free at 24 months (HR for disease recurrence or death, 0.20; 99.12% CI, 0.14-0.30; P < .001).

Myung-Ju Ahn, MD

Tetsuya Mitsudomi, MD, PhD

Tony SK Mok, MD

TABLE. ADAURA Trial Snapshot

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Osimertinib (n = 339)</th>
<th>Placebo (n = 343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32%</td>
<td>28%</td>
</tr>
<tr>
<td>Female</td>
<td>68%</td>
<td>72%</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>64 (30-86)</td>
<td>62 (31-82)</td>
</tr>
<tr>
<td>AJCC stage</td>
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<tr>
<td>IB</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>II</td>
<td>34%</td>
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</tr>
<tr>
<td>IIIA</td>
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</tr>
<tr>
<td>EGFR mutation at randomization</td>
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<td></td>
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<tr>
<td>Exon 19 deletion</td>
<td>55%</td>
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<td>L858R</td>
<td>45%</td>
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<tr>
<td>p.Thr790Met</td>
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</tr>
<tr>
<td>Outcomes</td>
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<tr>
<td>Stage II-IIIA</td>
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<tr>
<td>Median DFS, months (95% CI)</td>
<td>19.6 (16.6-24.5)</td>
<td>HR, 0.17; 99.06% CI, 0.11-0.26; P &lt; .001</td>
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<tr>
<td>Stage IIIA</td>
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<td>Median DFS, months (95% CI)</td>
<td>27.5 (22.0-35.0)</td>
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<td>Patients who received adjuvant chemotherapy</td>
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<td>HR for disease recurrence or death (95% CI)</td>
<td>0.16 (0.10-0.26)</td>
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<tr>
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AJCC, American Joint Committee on Cancer; DFS, disease-free survival; NC, not calculable; NR, not reached; NSCLC, non–small cell lung cancer.

Postoperative Radiotherapy in Stage II NSCLC

Mitsudomi said that the Japan Society of Clinical Oncology is considering the need for postoperative radiotherapy for patients with stage II NSCLC, although the Japanese Society of Thoracic Surgeons (JSTS) does not have a formal guideline on this topic. He noted that this was the case even before the ADAURA study, which demonstrated the benefit of adjuvant osimertinib over placebo in patients with resected EGFR-mutated NSCLC.

“In contrast, in Japan, osimertinib has not yet been approved as an adjuvant treatment for EGFR-mutated NSCLC, but an application for this indication has been submitted.6 ”We can’t use any TKI for [patients with] EGFR-mutated [disease],” Tetsuya Mitsudomi, MD, PhD, said. Instead, Mitsudomi explained that for patients with stage IB disease without lymph node metastasis, tegafur and uracil (UFT) is used. UFT, an oral anticancer drug developed in Japan, consists of a combination of the 5-fluorouracil congener prodrug tegafur (tetrahydrofuranyl-5-fluorouracil) and uracil (1:4), with the uracil used to enhance the anticancer effects of tegafur.7,8 For patients with stage II and III NSCLC, Mitsudomi said a cisplatin doublet, such as cisplatin plus vinorelbine, is typically used. This is the preferred regimen, as cisplatin plus pemetrexed did not show benefit.

Institution, like Lu’s, administers adjuvant chemotherapy to patients with high-risk disease, which she said is any patient with a tumor measuring greater than 4 cm. For patients with EGFR mutations, Ahn said osimertinib is the only TKI approved in South Korea for these patients but is not yet reimbursed.

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Wu said that although these findings demonstrated the relapse rate to be reduced by 80%, they are not related to the use of adjuvant chemotherapy (TABLE). Tony SK Mok, MD, unpacked this further, noting that although ADAURA is one of the most important studies in the past few years in terms of EGFR TKI benefit, “it’s not that the TKIs are not effective.” He noted that the ADAURA findings demonstrated the benefit to be reduced by 80%, but this was not due to the use of adjuvant chemotherapy, as the patients in the placebo arm continued to receive postoperative chemotherapy.

Tony SK Mok, MD
of moving treatment forward for patients with resectable EGFR-mutated NSCLC, it is not without some controversy. For example, he noted one challenge is with the trial design, which made chemotherapy optional before randomization, leading to confusion about chemotherapy.

“Where should we not give chemotherapy before we give osimertinib? How do we decide whether to give chemotherapy?” Mok said.

Ahn explained that controversy over when to use chemotherapy remains in South Korea. However, she emphasized that chemotherapy is the only treatment to show a survival benefit thus far, albeit low (4%-5%). Subsequently, she said chemotherapy should be given before osimertinib whenever possible but noted that this has been difficult to put into practice because many patients prefer oral agents. In such cases, she said giving osimertinib without chemotherapy is acceptable because analyses have shown a DFS benefit regardless of whether chemotherapy is administered.

Mitsudomi agreed with this approach. “We should give chemotherapy because of the design of studies such as [ADARUA]. The study showed that osimertinib is beneficial even without chemotherapy. So if a patient refused [chemotherapy], they are not fit to receive cisplatin-based therapy, or they are too old, then I’m happy to keep osimertinib alone,” he said.

Mok proceeded to ask the panelists whether any first-generation EGFR TKIs such as gefitinib or icotinib, which are both approved in China, still have a role in the adjuvant treatment of EGFR-mutated resectable NSCLC in the osimertinib era. Lu noted these first-generation agents continue to be used in China because they are reimbursed, whereas osimertinib is not.

In terms of OS, he said none of the first-generation agents have shown an OS benefit but they delay disease progression. In data from a 2021 meta-analysis by Chinese investigators that included data from 5 studies examining various EGFR TKIs as adjuvant therapy in EGFR-positive early-stage NSCLC (stage IB to IIA), the HR for DFS was 0.38 (95% CI, 0.22-0.63), in favor of EGFR TKIs.¹ The studies in the meta-analysis included ADARUA assessing osimertinib, ADJUVANT/CTONG104 and Li 2014 assessing gefitinib, and EVAN (NCT01683175) and RADIANT (NCT00373425) assessing erlotinib (Tarceva). All studies except for ADARUA were included in the OS analysis, which revealed a 39% reduction in the risk of all-cause death in patients treated with adjuvant EGFR TKIs compared with those in control groups, but this finding did not reach statistical significance (HR, 0.61; 95% CI, 0.31-1.22).³ Survival data for osimertinib are still awaited. Mok suspects they may show an OS benefit vs the first-generation agents, because osimertinib has been shown to penetrate the central nervous system (CNS). “I predict the CNS protection will probably contribute to the overall benefit of the drug,” he said. Wu agreed, noting that a model developed to predict OS based on the available ADARUA trial data suggest an OS benefit.

MOLECULAR TESTING IN POSTOPERATIVE NSCLC

When discussing the use of routine molecular testing following surgical resection, in addition to testing for EGFR mutations, Lu said he will test for ALK gene rearrangements, which have been observed in 4% to 5% of patients with NSCLC.¹²,¹³ He explained these patients tend to relapse quickly with adjuvant chemotherapy but ALK-positive tumors respond well to small-molecule ALK inhibitors, so he tries to identify candidates for this treatment. He mentioned enrolling patients in the ongoing phase 3 ALINA trial (NCT03456076), in which investigators are evaluating the efficacy and safety of alectinib (Alecensa) compared with platinum-based chemotherapy in the adjuvant setting for patients with stage IB to IIIA ALK-positive NSCLC.¹³ The trial has completed enrollment.

Mitsudomi said molecular testing before a recurrence is not routinely done in Japan because treatment options remain limited. “We can’t use gefitinib, osimertinib, alecitinib, or any of these kinds of drugs after the surgery. They are not approved [or] reimbursed. That rule is very strict in Japan,” he said. Nevertheless, he said some physicians in Japan will proactively test patients with advanced disease who are at high risk of recurrence so they can plan the next treatment for when the patient recurs following adjuvant chemotherapy. In South Korea, Ahn said she routinely tests patients for EGFR mutations, ALK gene rearrangements, and PD-L1 to prepare for when patients relapse. She noted that before the ADARUA data, South Korea used to follow a similar testing approach to Japan.

MULTIDISCIPLINARY CARE AND NEOADJUVANT THERAPY

The panelists differed significantly in when they involve the multidisciplinary team (MDT). Lu said all stage II and III cases at his institution in China are discussed with an MDT. “For stage I, we have so many patients [right now]. We do not have enough time for every patient to do the MDT,” he said.

Ahn said mostly patients with stage III disease are discussed by the MDT at her institution in South Korea. “[It’s] very selective—patients who cannot judge by themselves,” she said. Mitsudomi said MDT is rarely done at his institution in Japan for those with resectable disease, including stage III. “In very special cases, we may have the discussion, but usually we do not have any discussion,” he said.

Mok said his institution in Hong Kong follows a similar practice, with only selective cases put through MDT. “It’s [mostly] case-based because it’s impossible to go through every case in a very busy clinic like ours,” he said.

In terms of neoadjuvant therapy, practices also varied significantly between the panelists. Both Wu and Lu said they will use neoadjuvant TKI in appropriate patients. For example, Lu said that for patients who have marginally resectable disease, the routine practice is still to recommend chemoradiation. Additionally, at his institution, chemotherapy plus immunotherapy is used in the neoadjuvant setting based on data from CheckMate 816 trial (NCT02998528), which compared neoadjuvant nivolumab (Opdivo) plus ipilimumab (Yervoy) vs nivolumab plus chemotherapy vs chemotherapy alone in early-stage NSCLC.¹⁰,¹¹ A statistically significant improvement in pathological complete response was observed with neoadjuvant nivolumab plus chemotherapy without impeding the feasibility or timing of surgery or affecting the extent or completeness of the resection vs chemotherapy alone. These data supported the use of nivolumab plus chemotherapy as a potential neoadjuvant option for patients with stage IB to IIIA resectable NSCLC.¹²

Ahn and Mitsudomi said they never use neoadjuvant TKIs. “A long time ago, we did a small phase 2 study with erlotinib as our neoadjuvant [agent],” Ahn said. “[Patients were] not molecularly selected, but clinically selected. We didn’t have good results.” She said investigators have not followed neoadjuvant TKI with an adjuvant TKI, and she finds this approach insufficient. “We should give another TKI [after surgery],” she said. Mitsudomi said he does not have any neoadjuvant TKIs available in Japan. Subsequently, tumors that are not resectable will be treated with concurrent radiation therapy, which may be followed by surgery if the tumor becomes resectable.

For a full list of references, see the article at OncLive.com.
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