OncLive® Celebrates 14 Leaders in Cancer Care

PEER EXCHANGE®
Will Slow and Steady Progress in Treating SCLC Win the Race?

OncPathways®
PSMA-Targeting Radiopharmaceuticals Are Poised for Expansion in PROSTATE CANCER

SOCIETY OF HEMATOLOGIC ONCOLOGY 2021 ANNUAL MEETING
Updates From Pivotal Studies in MYELOMA, CLL, and AML

CLINICAL PERSPECTIVES
Sara M. Tolaney, MD, MPH, Discusses How De-escalation Strategies May Improve Outcomes in HER2+ BREAST CANCER

GLOBAL LIVER INSTITUTE
Pivotal Trial Results Look to Shake up HCC Treatment Landscape
By Amit Mahipal, MBBS, and Richard Kim, MD
IN ER+/HER2- METASTATIC BREAST CANCER (mBC)

CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

Complex mechanisms of estrogen receptor (ER) signaling have been associated with tumor growth.1-3
In ER+/HER2- mBC, the ER pathways are involved in tumor progression and treatment escape mechanisms that enable endocrine resistance.\textsuperscript{1,2,4,5}

To strengthen the fight against resistance, could advancements in ER antagonism and degradation help decrease the ER pathway’s downstream effects?

**References:**

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Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 68.
IO Combo Anchors a New Front Line
Taking Shape in Unresectable HCC

by ANITA T. SHAFFER

In the past few years, positive data from phase 3 trials have begun to turn the tide for therapeutic regimens for patients with hepatocellular carcinoma (HCC). Although sorafenib (Sutent) kicked off improved outcomes, the introduction of the immuno-oncology (IO) combination atezolizumab (Tecentriq) plus bevacizumab (Avastin) has become the preferred standard for first-line systemic therapy.

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By Maurie Markman, MD

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Join Ajai Chari, MD, to learn more about recent advancements in the oncology treatment landscape with this iPub® on immuno-oncology and the Bispecific T-Cell Engager (BiTE®) technology, a novel targeted immuno-oncology platform.1 BiTE® molecules are designed to engage the cytotoxic potential of the body’s endogenous T cells to various tumor-specific antigens to target and help eliminate detectable cancer cells.2,3

In this iPub®, Dr Chari will highlight the targets of some of the investigational BiTE® molecules, including B-cell maturation antigen in multiple myeloma and prostate-specific membrane antigen in prostate cancer, as well as other emerging targets in the BiTE® immuno-oncology platform.4

References
Innovators of Change Are Honored as 2021 Giants

ONCE A YEAR ONCOLOGYLIVE® CELEBRATES the Giants of Cancer Care®, a class of pioneers whose groundbreaking achievements establish the foundation for future advances. The 2021 class of winners is an esteemed group of 14 innovators in oncology research and clinical practice who have made landmark contributions to the field.

Several of this year’s honorees were members of investigative teams that revolutionized the treatment landscape. For example, Robert C. Young, MD, whose research has spanned tumor types, was part of the “Gang of Five,” a group of investigators at the National Cancer Institute who developed the first curative regimens for Hodgkin lymphoma and diffuse aggressive lymphomas, specifically the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) protocol. He is the winner of this year’s gynecologic category.

Michael B. Atkins, MD, the winner in the melanoma category, was at the helm of investigative efforts that helped to establish dual-checkpoint blockade with antibodies against both PD-1 and CTLA-4 as the standard of care in melanoma. The nivolumab (Opdivo)/ipilimumab (Yervoy) combination induces extended treatment-free melanoma remissions in more than 50% of patients.

Though we celebrate their achievements as leading investigators for oncologic therapies, their never-failing contributions outside of their respective fields deserve recognition as well. As the COVID-19 pandemic became top of mind for all health care professionals, Toni K. Choueiri, MD, the winner in the genitourinary cancer category turned his attention to a multinational study to identify COVID-19 risk factors unique to patients with cancer. The results of the CCC19 study (NCT04354701) showed that patients with cancer and COVID-19 had increased risk for 30-day all-cause mortality.

The 9th Annual Giants of Cancer Care® hybrid awards ceremony will take place on Thursday, November 4, 2021. The live event will be held at the New York Marriott Marquis as part of the 39th Annual Chemotherapy Foundation Symposium® (CFS®). We hope you join us in celebrating the entire 2021 Giants of Cancer Care® class:

• Breast Cancer- Nancy E. Davidson, MD
• Community Outreach/Cancer Policy- Julie R. Gralow, MD
• Gastrointestinal Cancer- Daniel G. Haller, MD
• Genitourinary Cancer- Toni K. Choueiri, MD
• Gynecologic Cancer- Robert C. Young, MD
• Leukemia- Richard M. Stone, MD
• Lung Cancer- Pasi A. Jänne, MD, PhD
• Lymphoma- Steven T. Rosen, MD
• Melanoma- Michael B. Atkins, MD
• Myeloma- Paul G. Richardson, MD
• Pediatric Oncology- Richard J. O’Reilly, MD
• Prevention/Genetics- Matthew L. Meyerson, MD, PhD
• Radiation Oncology- Walter J. Curran Jr, MD
• Supportive, Palliative, and/or Geriatric Care - Dawn L. Hershman, MD, MS

As always, thank you for reading.
Mike Hennessy Sr
Chairman and Founder

We invite you to join us as your peers are recognized as Giants of Cancer Care®. To RSVP, scan the QR code or visit bit.ly/3kpqn2X.
BETTER IS HOME TO NEW JERSEY’S BEST CANCER CENTER

U.S. News & World Report has recognized Hackensack Meridian John Theurer Cancer Center at Hackensack University Medical Center as the best cancer center in all of New Jersey. And as a member of one of just 16 NCI-designated cancer consortia, we have distinguished ourselves as New Jersey’s premier cancer center—offering nationally recognized cancer specialists, clinical trials and immunotherapy including CAR T-Cell.

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
HE CONTINUED UNCERTAINTIES OF the current and future status of the COVID-19 pandemic have resulted in a lack of trust in the authority of the scientific establishment in the United States, and elsewhere, as it operates during these difficult times. Some of the top concerns are the eventual development of 1 or more vaccine-resistant mutants, the unknowns associated with the long-awaited return of in-person schooling for yet-to-be vaccinated children, a reduction in social distancing as declining temperatures result in more indoor interactions, and the anticipated uptick in travel during the holiday season. All of these pose difficult scenarios for which the scientific community has few, if any, objectively solid answers to guide policy makers and the general public.

Unfortunately, today we must add to this list the distressing politicization of the evolving science associated with the pandemic and the uncomfortable place public health care officials find themselves in attempting to advise based on, what they consider to be, the best available data. Further, although it is painful to acknowledge, in recent times government scientists, public health officials, and organizations—such as the FDA and the CDC, which were previously recognized to have complete independence to speak the truth as they saw it—appear to have been compromised by their nonscientific bosses. At times it may appear that the statements and actions of these officials represent the political spin of the day, devoid of essential rigorous scientific review and debate before conclusions are drawn and communicated to the public.

Some in the scientific community appear to have made matters worse by rendering strong public statements offering opinions related to the ethics of vaccine booster shots vs sending a much larger proportion of vaccine product to countries that, for several reasons, continue to have woefully inadequate immunization rates.1 The issue is not the right of individual scientists to voice their personal opinions regarding this topic but rather the training or expertise that members of the scientific community possess to provide expertise related to ethical considerations.

Additionally, there is continuing uncertainty about the origin of the SARS-COV-2 virus and the disquieting evidence of potential conflict of interest among several highly regarded members of the scientific community in expressing their thoughts on the relation of the outbreak to an accidental lab leak.2-4

Finally, science does not follow a well-defined script. What may be considered the best available evidence today can easily and appropriately change tomorrow based on newer or more robust studies, extended observations associated with previously reported results, or even challenges to the quality, objectivity, or honesty of prior investigative efforts. The scientific process is just that, a process. Simple definitive answers may not be available, as critically relevant and potentially complex public health questions and recommendations—no matter how strongly evidence based—may conflict with the values, beliefs, and economic welfare of individuals, families, and societal groups.

The concern highlighted here is for how the overall response to the COVID-19 pandemic by the scientific community may ultimately affect the views of the American public, both the authority of public health officials and objectively validated clinical science in the cancer arena. Today, in the United States, we continue to see the proliferation of effective but ever more expensive antineoplastic strategies. As many cancers become more like chronic diseases where treatment may be delivered for years rather than months, it is increasingly clear this system will not be sustainable. One possible solution will be major changes in societal attitudes regarding cancer prevention (eg, vaccination) and personal lifestyle.

“Science does not follow a well-defined script...The scientific process is just that, a process.”
A recent modeling report has suggested that elimination of cervical cancer in this country will be possible within the next several decades. This projection assumes an effective nationwide human papillomavirus vaccination strategy and societal efforts to reduce poverty-related disparities in many regions of the country. Clearly, the clinical and economic effect associated with successful strategies would be substantial. Leaders in cancer care and scientific establishments are best positioned to helm such an effort, assuming the public puts its trust in their recommendations.

Or consider for a moment a recent report from the World Health Organization that claimed as many as 4% of all cancer cases worldwide in 2020 resulted from alcohol consumption, with almost half of this total due to individuals who drank excessively. This analysis suggested that in 39% of men who developed esophageal cancer and 4.5% of women who developed breast cancer, alcohol consumption played an influential role. Imagine the effect on the number of lives lost from a meaningful reduction in heavy alcohol consumption. Who should lead this effort other than the cancer clinical and research community?

Similarly, the influence of obesity on cancer risk has been well documented in scientific literature, with one-third of the world population considered to be either overweight or obese. The incidence of several cancers, including endometrial, esophageal, pancreatic, kidney, thyroid, colon, and postmenopausal breast cancers, has been shown to increase in individuals with excessive body mass. Again, imagine the potential effect of a coordinated decade-plus national/international campaign to modify diets and establish economic incentives to produce food products that will reverse the deadly trend.

Leaders of the cancer establishment should be in the forefront of efforts to make these difficult but essential changes. But this can happen only if the public puts its trust and faith in scientifically based pronouncements and objectively validated and nonpolitically motivated recommendations of that leadership.

REFERENCES
FDA Grants Ivosidenib Indication in IDH1-Mutant Cholangiocarcinoma

Oral ivosidenib (Tibsovo) has been approved by the FDA for adult patients with previously treated, locally advanced, or metastatic cholangiocarcinoma with an IDH1 mutation. Further, the FDA approved the Oncomine Dx Target Test developed by Life Technologies Corporation as a companion diagnostic device to aid in selecting patients with cholangiocarcinoma for treatment with ivosidenib.

Investigators assessed the efficacy of ivosidenib in the randomized phase 3 ClariDHy trial (NCT02989857), which included 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation who experienced disease progression after at least 1 regimen containing gemcitabine or 5-fluorouracil. Patients could have a maximum of 2 prior therapies. Results demonstrated that the Bruton tyrosine kinase inhibitor elicited a 77.5% response rate (95% CI, 68.1%-85.1%) in cohort 1 and a 50% response rate (95% CI, 29.9%-70.1%) in cohort 2. Response was reported as combined complete, very good, and partial response rates. The event-free survival rate at 12 months was 94.4% (95% CI, 85.8%-97.9%). The FDA evaluated the data based on standard consensus response criteria from the International Workshop on Waldenström’s Macroglobulinemia-6 criteria.

Of note, the data concerning the efficacy of zanubrutinib from cohort 1 of the ASPEN trial did not meet statistical significance of the prespecified outcome of very good partial response or better in the intention-to-treat population.

FDA Shakes Up Pembrolizumab Indication for Urothelial Carcinoma

The FDA has granted full approval to pembrolizumab (Keytruda) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who were not candidates to receive cisplatin-containing chemotherapy and whose tumors had a PD-L1 expression of a combined positive score of 10 or higher, per an FDA-approved test, or in those who were not eligible to receive any platinum-containing chemotherapy irrespective of PD-L1 status.

The label update follows the FDA’s Oncologic Drugs Advisory Committee vote in April 2021 to uphold the accelerated approval of pembrolizumab for the frontline treatment of patients with cisplatin- and carboplatin-ineligible locally advanced or metastatic urothelial carcinoma.

The review was issued after the confirmatory phase 3 KEYNOTE-361 trial (NCT02853305) did not meet its prespecified end points of overall survival or progression-free survival vs standard-of-care chemotherapy. In the study investigators evaluated pembrolizumab as a monotherapy and in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic urothelial carcinoma who were eligible for platinum-containing chemotherapy.

NCCN Issues Guidance Update on COVID-19 Booster for Patients With Cancer

After a review of the latest data and guidance from the FDA and the CDC, the National Comprehensive Cancer Network (NCCN) has updated the COVID-19 guidelines. The updated recommendations include a list of patients eligible for the recommended third dose of the mRNA COVID-19 vaccine. These include:

- Patients with new or recurring solid tumors who received treatment within 1 year of their initial vaccine dose, regardless of their type of cancer therapy.
- Patients with active hematologic malignancies regardless of whether they are currently receiving cancer therapy.
- Individuals who received a stem cell transplant (SCT) or engineered cellular therapy (chimeric antigen receptor T cells), especially those who underwent treatment in the past 2 years.
- Any recipients of allogeneic SCT on immunosuppressive therapy or with a history of graft-vs-host disease regardless of the time of transplant.
- Individuals with an additional immunosuppressive condition, such as HIV, or those who are being treated with immunosuppressive agents unrelated to their cancer therapy.

For those who are eligible, the NCCN follows the CDC recommendation that individuals wait at least 4 weeks between the second and third COVID-19 vaccine doses. Individuals who develop COVID-19 should have documented clearance of the virus prior to receiving a third dose. Of note, the guidance also recommends that individuals who meet these criteria receive the third dose in a health care setting to limit their exposure to the general population.

FDA Digest

Zanubrutinib Receives OK for Waldenström Macroglobulinemia

The FDA has approved zanubrutinib (Brukinsa) for the treatment of adult patients with Waldenström macroglobulinemia. The agency approved the drug based on a noncomparative assessment of response and event-free survival rates of the zanubrutinib arms from 2 cohorts of the phase 3 ASPEN trial (NCT03053440). Cohort 1 included 102 patients with MYD88 L265P-mutant Waldenström macroglobulinemia treated with zanubrutinib; cohort 2 included 26 response-evaluable patients with MYD88 wild-type disease.

Results demonstrated that the Bruton tyrosine kinase inhibitor elicited a 77.5% response rate (95% CI, 68.1%-85.1%) in cohort 1 and a 50% response rate (95% CI, 29.9%-70.1%) in cohort 2. Response was reported as combined complete, very good, and partial response rates. The event-free survival rate at 12 months was 94.4% (95% CI, 85.8%-97.9%). The FDA evaluated the data based on standard consensus response criteria from the International Workshop on Waldenström’s Macroglobulinemia-6 criteria.

Of note, the overall survival data compared with placebo was not significant (HR, 0.79; 95% CI, 0.56-1.12; P = .093). The objective response rates were 2.4% and 0%, respectively.

In total, 70% of patients randomized to placebo crossed over to receive zanubrutinib after radiographic disease progression.

FDA Shakes Up Pembrolizumab Indication for Urothelial Carcinoma

The FDA has granted full approval to pembrolizumab (Keytruda) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-based chemotherapy. This conversion from an accelerated approval also revises the prior indication, which specified treatment for patients with locally advanced or metastatic urothelial carcinoma who were not candidates to receive cisplatin-containing chemotherapy and whose tumors had a PD-L1 expression of a combined positive score of 10 or higher, per an FDA-approved test, or in those who were not eligible to receive any platinum-containing chemotherapy irrespective of PD-L1 status.

The label update follows the FDA’s Oncologic Drugs Advisory Committee vote in April 2021 to uphold the accelerated approval of pembrolizumab for the frontline treatment of patients with cisplatin- and carboplatin-ineligible locally advanced or metastatic urothelial carcinoma.

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TO READ MORE, VISIT bit.ly/3z6idNq.

TO READ MORE, VISIT bit.ly/3tPDr4R.

TO READ MORE, VISIT bit.ly/31PDr4R.
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Cemiplimab Earns High Marks in First-Line Treatment of Advanced NSCLC

by KYLE DOHERTY

ON FEBRUARY 22, 2021, THE FDA approved the PD-1 inhibitor cemiplimab-rwlc (Libtayo) for the first-line treatment of patients with advanced non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score ≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations. Advanced disease was defined as patients who are not candidates for surgical resection, definitive chemoradiation, or who have metastatic disease.

The approval was based on data from the phase 3 EMPOWER-Lung 1 trial (NCT03088540), which showed that patients treated with cemiplimab (n = 356) experienced an overall response rate (ORR) of 37% (95% CI, 32%-42%) compared with 21% (95% CI, 17%-25%) in patients treated with chemotherapy (n = 354). Notably, the median duration of response (DOR) was much higher in the cemiplimab cohort, registering at 21.0 months (1.9+ to 23.3+) compared with 6.0 months (1.3+ to 16.5+) for patients treated with chemotherapy. The median overall survival (OS) in the cemiplimab group was 22.1 months (95% CI, 17.7-not estimable) vs 14.3 months (95% CI, 11.7-19.2) in the chemotherapy group (HR, 0.68; 95% CI, 0.53-0.87; P = .0022). In an interview with OncologyLive®, Ahmet Sezer, MD, a professor in the Department of Medical Oncology at Başkent University in Ankara, Turkey, discussed how the approval of cemiplimab could potentially make a huge impact for patients with advanced NSCLC.

What makes cemiplimab a novelty in the advanced NSCLC setting?

Cemiplimab is a fully humanized monoclonal antibody targeting the immune checkpoint receptor PD-L1 on T cells. Like other PD-1 inhibitors cemiplimab binds to PD-1 and has been shown to block cancer cells from using the pathway to suppress T-cell activation. In advanced NSCLC, PD-1 inhibitors have become a key component of the treatment of patients with advanced NSCLC without EGFR, ALK, or ROS1 mutations. However, there is still a need to optimize chemotherapy treatment options for patients with high PD-L1 expression levels.

In this pivotal phase 3 trial, EMPOWER-Lung 1, cemiplimab demonstrated an impressive level of efficacy and was superior in extending OS compared with chemotherapy. This reinforces the potential of cemiplimab as a valuable treatment option for appropriate patients with advanced NSCLC with PD-L1 expression of at least 50%. The safety profile of cemiplimab is consistent with the previous 2 reported trials. To summarize, these results support cemiplimab as a new monotherapy option for patients with first-line advanced NSCLC with a PD-L1 expression of at least 50%. The safety profile of cemiplimab is consistent with the previous 2 reported trials.

How will this approval affect the treatment paradigm for patients with NSCLC with high PD-L1 expression?

Physicians, myself included, who treat [patients with] NSCLC are a data-driven group and appreciate having multiple treatment options. Given the impressive level of efficacy demonstrated in the EMPOWER-Lung 1 trial, I believe cemiplimab has the potential to make a meaningful difference for the many patients battling these difficult-to-treat cancers. Additionally, [data from] EMPOWER-Lung 1 helps address current gaps in knowledge surrounding advanced NSCLC treatment, because it allows for certain patient and disease characteristics particularly underrepresented in [other] advanced NSCLC trials.

Are there any unanswered questions with the agent that future research should address?

We see many different patients with advanced NSCLC. Each patient is unique, and they can have a variety of disease characteristics that need to be considered. In short, there is still a lot we don’t know about advanced NSCLC treatment, and more research is always needed. However, I believe EMPOWER-Lung 1 is an important step and offers physicians valuable new data that can help them in treating various patients they come across in daily clinical practice.

REFERENCES


Please elaborate on the efficacy and toxicity data that were observed in EMPOWER-Lung 1.

EMPOWER-Lung 1 compared first-line cemiplimab monotherapy with platinum-based chemotherapy in patients with advanced NSCLC with PD-L1 expression of at least 50%. The primary end points were OS and provision for survival. Secondary end points included ORR, DOR, and safety.

Cemiplimab demonstrated impressive efficacy early on and EMPOWER-Lung 1 was stopped early because of a highly significant improvement in OS compared with chemotherapy. Specifically, cemiplimab reduced the risk of death by 33% among all patients, and 43% in those with PD-L1 expression of at least 50%. These results were achieved with a greater than 50% crossover rate to cemiplimab following disease progression on chemotherapy. [Additionally, this is] the largest population of patients with pretreated and stable brain metastases among advanced NSCLC [included in a] pivotal trial to date.

To summarize, these results support cemiplimab as a new monotherapy option for patients with first-line advanced NSCLC with a PD-L1 expression of at least 50%. The safety profile of cemiplimab is consistent with the previous 2 reported profiles of the agent and other PD-L1 inhibitors in NSCLC and other tumor types. Additional details have been published in The Lancet.
**PIVOTAL CLINICAL TRIAL**

EMPower-Lung 1 (NCT03088540) was a phase 3 randomized, multicenter, open-label, active-controlled study of cemiplimab vs chemotherapy as first-line treatment for patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC.

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 (31-79) N = 356</td>
</tr>
<tr>
<td>64 (40-84) N = 354</td>
</tr>
</tbody>
</table>

**Brain metastases (%)**

<table>
<thead>
<tr>
<th></th>
<th>Cemiplimab arm</th>
<th>Chemotherapy arm</th>
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</thead>
<tbody>
<tr>
<td>%</td>
<td>12.4%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

**Cancer stage at screening (%)**

<table>
<thead>
<tr>
<th></th>
<th>Cemiplimab arm</th>
<th>Chemotherapy arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>82.3%</td>
<td>85.3%</td>
</tr>
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</table>

**Histology (%)**

<table>
<thead>
<tr>
<th></th>
<th>Cemiplimab arm</th>
<th>Chemotherapy arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>44.7%</td>
<td>53.3%</td>
</tr>
</tbody>
</table>

**CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; NE, not estimable.**

**EFfICACY RESULTS IN EMPOWER-LUNG 1**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cemiplimab (n = 356)</th>
<th>Chemotherapy (n = 354)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>22.1 (17.7-NE)</td>
<td>14.3 (11.7-19.2)</td>
</tr>
<tr>
<td>HR, 0.68; 95% CI, 0.53-0.87; P = .0022</td>
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</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.2 (4.5-8.3)</td>
<td>5.6 (4.5-6.1)</td>
</tr>
<tr>
<td>HR, 0.59; 95% CI, 0.49-0.72; P &lt; .0001</td>
<td></td>
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</tr>
<tr>
<td>ORR (95% CI)</td>
<td>37% (32-42%)</td>
<td>21% (17-25%)</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
<td>1%</td>
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<tr>
<td>PR</td>
<td>33%</td>
<td>20%</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>21.0 (1.9-23.3+)</td>
<td>6.0 (1.3-16.5+)</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

- **Immune-mediated adverse reactions**: may be severe or fatal and can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue cemiplimab based on the severity of reaction.
- **Infusion-related reaction**
- **Complications of allogeneic hematopoietic stem cell transplantation**
- **Embryo-fetal toxicity**

**COMMONLY REPORTED ADVERSE EFFECTS IN EMPOWER-LUNG 1**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Cemiplimab (n = 355)</th>
<th>Chemotherapy (n = 342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muskuloskeletal pain</td>
<td>26%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Rash</td>
<td>15%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>15%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11%</td>
<td>5%</td>
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<tr>
<td>Cough</td>
<td>11%</td>
<td>0%</td>
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<tr>
<td>Grade 3/4</td>
<td></td>
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</tr>
<tr>
<td>Muskuloskeletal pain</td>
<td>0.6%</td>
<td>27%</td>
</tr>
<tr>
<td>Rash</td>
<td>1.4%</td>
<td>6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.4%</td>
<td>50%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.1%</td>
<td>26%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0.6%</td>
<td>18%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Cough</td>
<td>0%</td>
<td>8%</td>
</tr>
</tbody>
</table>

**REFERENCES**

The first and only FDA-approved treatment, in combination with 5-FU/LV, for metastatic pancreatic cancer after gemcitabine-based therapy, proven to extend overall survival (OS)¹

**INDICATION**

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

**WARNING: SEVERE NEUTROPenia and SEVERE DIARRHEA**

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

**CONTRAINDICATION**

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

**WARNINGS AND PRECAUTIONS**

**Severe Neutropenia**

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE + 5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE + 5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

**Severe Diarrhea**

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset ≥24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE + 5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE + 5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

**Interstitial Lung Disease (ILD)**

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

**Severe Hypersensitivity Reactions**

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

**Embryo-Fetal Toxicity**

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during and for 1 month after ONIVYDE treatment.

**ADVERSE REACTIONS**

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%,

Please see additional Important Safety Information throughout and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.
ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST- GEMCITABINE METASTATIC PANCREATIC CANCER‡

FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE†

†Liposomal irinotecan + 5-FU/LV is the only Category 1 National Comprehensive Cancer Network® (NCCN®) chemotherapy recommendation for patients with post-gemcitabine metastatic pancreatic cancer with good performance status and disease progression.‡ NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

†NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m² every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were progression-free survival and objective response rate.†‡

DRUG INTERACTIONS
Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme–inducing therapies 22 weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy.

USE IN SPECIFIC POPULATIONS
Pregnancy and Reproductive Potential
Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

Lactation
Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

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

DOSAGE AND ADMINISTRATION
The recommended dose of ONIVYDE is 70 mg/m² intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD. Do not substitute ONIVYDE for other drugs containing irinotecan HCl.


For more information, visit ONIVYDEinfo.com
ONIVYDE® (irinotecan liposome injection) for intravenous use

Initial U.S. Approval: 1996

**BRIEF SUMMARY:** refer to full Prescribing Information for complete product information.

1. **INDICATIONS AND USAGE**

ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

**Limitation of Use:** ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas (see Clinical Studies, 14).

**WARNING:** SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE®. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. (see Dosing and Administration 2.2, 5.1)

Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity. (see Dosing and Administration 2.2, see Warnings and Precautions 5.2)

**4 CONTRAINDICATIONS**

ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

**5 WARNINGS AND PRECAUTIONS**

5.1 **Severe Neutropenia:** ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosage and Administration, 2.2).

5.2 **Severe Diarrhea:** ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) (see Cholinergic Reactions, 6.1). An individual patient may experience both early- and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose (see Dosage and Administration, 2.2).

5.3 **Interstitial Lung Disease (ILD):** Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

5.4 **Severe Hypersensitivity Reaction:** Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

5.5 **Embryo-Fetal Toxicity:** Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1).

**6 ADVERSE REACTIONS**

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- **Severe Neutropenia** (see Warnings and Precautions, 5.1; Boxed Warning)
- **Severe Diarrhea** (see Warnings and Precautions, 5.2; Boxed Warning)
- **Interstitial Lung Disease** (see Warnings and Precautions, 5.3)
- **Severe Hypersensitivity Reactions** (see Warnings and Precautions, 5.4)

6.1 **Clinical Trials Experience**

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and S-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/S-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and S-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (S-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dl, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/S-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the S-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥20%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/S-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/S-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/S-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
ONIVYDE®. Severe or life-threatening neutropenic fever or sepsis (see Clinical Studies, 14)

4 CONTRAINDICATIONS

- Diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with early diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction)
- FU)
- leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count (ANC) is below 1500/mm3 or if neutropenic fever occurs.
- Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm3 or if neutropenic fever occurs.
- The incidence of Grade 3 or 4 late-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV.
- The following adverse drug reactions are discussed in greater detail in Warnings and Precautions, 5.2; Boxed Warning
- A comparison of adverse drug reactions as Grades 1–4 or ≥2% Difference for Grades 3–4 in the ONIVYDE®/5-FU/LV Arm
- A comparison of adverse drug reactions as Grades 1–4 or ≥2% Difference for Grades 3–4 in the 5-FU/LV Arm
- The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥5% difference Grades 3–4 [severe] according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/5-FU/LV (n=117) vs 5-FU/LV (n=134)
- Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement.
- Hematologic: anemia (any 97%, 86%); severe 6%, 5%); lymphopenia (any 81%, 75%); severe 27%, 17%); neutropenia (any 52%, 6%); severe 20%, 2%); thrombocytopenia (any 41%, 33%); severe 2%, 0%)
- Hepatic: increased alanine aminotransferase (any 51%, 37%); severe 6%, 1%); hyperalbuminemia (any 43%, 30%); severe 2%, 0%)
- Metabolic: hypomagnesemia (any 35%, 21%); severe 0%, 0%); hypokalemia (any 32%, 19%); severe 2%, 2%); hypercalcemia (any 32%, 20%); severe 1%, 0%); hyperphosphatemia (any 29%, 18%); severe 4%, 1%); hyponatremia (any 27%, 12%); severe 5%, 3%)
- Renal: increased creatinine (any 18%, 13%); severe 0%, 0%)

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy (see Clinical Pharmacology, 12.3)

7.2 Strong CYP3A4 or UGT1A1 Inhibitors: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE® with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE® therapy (see Clinical Pharmacology, 12.3)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy, Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m2 in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

8.2 Lactation, Risk Summary: There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk (see Data in the full Prescribing Information).

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE®, advise a nursing woman not to breastfeed during treatment with ONIVYDE® and for 1 month after the final dose.

8.3 Females and Males of Reproductive Potential, Contraception, Females: ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations, 8.1). Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month after the final dose. Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE® and for 4 months after the final dose (see Nonclinical Toxicology, 13.1).

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

8.5 Geriatric Use: Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/5-FU/LV in Study 1, 49% were ≥65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE®.

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ONV-US-000700 v2.0
**IO Combo Anchors a New Front Line Taking Shape in Unresectable HCC**

by ANITA T. SHAFFER

**THE TIDE IS STARTING** to turn toward more effective frontline systemic therapies for patients with unresectable hepatocellular carcinoma (HCC) as a result of the introduction of a novel immune-oncology (IO) combination. There is also the prospect of more innovative therapies in the pipeline, according to liver cancer experts. At the same time, patients are receiving systemic therapies earlier in the course of their disease, resulting in an across-the-board improvement in outcomes.

The combination of atezolizumab (Tecentriq) plus bevacizumab (Avastin) has become the preferred standard for first-line systemic therapy for unresectable disease in several treatment guidelines, including those of the National Comprehensive Cancer Network (for Child-Pugh Class A disease) and European Society for Medical Oncology.1,2

The regimen demonstrated superiority over sorafenib (Nexavar) in this patient population in the phase 3 IMbrave150 trial (NCT03434379), leading to FDA approval for the combination in May 2020.3 Two other therapies, an IO combination of sintilimab plus a bevacizumab biosimilar, and monotherapy with donafenib, a multikinase inhibitor, also have shown improvement over sorafenib in late-stage study results published this year.4,5

“**ATEZOLIZUMAB PLUS BEVACIZUMAB**

The combination of checkpoint inhibition with atezolizumab, an anti–PD-L1 inhibitor, and bevacizumab, an antiangiogenic monoclonal antibody, is the first regimen to show a statistically significant improvement in overall survival (OS) as first-line therapy compared with single-agent sorafenib, Sangro said. In 2007, the FDA approved sorafenib, which inhibits multiple kinases including several involved in angiogenesis, for the treatment of patients with unresectable HCC based on findings from the phase 3 SHARP study (NCT00105443).2

Although sorafenib outcomes have proved difficult to beat, the median OS has increased in both the active and comparator arms in key frontline trials over the years, Sangro noted. The median OS was 10.7 months with sorafenib vs 7.9 months with placebo (HR, 0.69; \(P < .001\)) in the SHARP trial; 13.6 months for lenvatinib (Lenvima) vs 12.3 months with sorafenib (HR, 0.92; \(P \text{ not available}\)) in the REFLECT study (NCT01761266); 16.4 months with nivolumab (Opdivo) vs 14.7 months with sorafenib (HR, 0.85; \(P = .0752\)) in CheckMate 459 (NCT02576509); and not estimable (NE) with atezolizumab plus bevacizumab as first-line therapy,” Sangro said. “But at the same time, we have to acknowledge that TKIs do work in patients with HCC in the advanced stage. And that is not only that they work as cytostatics and for delayed tumor growth, but they... are able to induce objective remissions that are long lasting.”

Bruno Sangro, MD, PhD
vs 13.2 months with sorafenib (HR, 0.58; 2-sided \( P = .0006 \)) in primary findings from IMbrave150.\(^6\)

The FDA approved lenvatinib, a multitargeted kinase inhibitor, for the first-line treatment of patients with unresectable HCC based on its noninferiority to sorafenib in the REFLECT trial. The agency had granted an accelerated approval for nivolumab, a PD-1 inhibitor, in the second-line setting but Bristol Myers Squibb voluntarily withdrew the indication after the immunotherapy agent failed to achieve statistical significance over sorafenib for OS in CheckMate 459.\(^7,8\)

The improvements in sorafenib efficacy across trials reflect changes in the patient populations considered eligible for systemic therapy, Sangro said. Whereas the SHARP trial enrolled patients with unresectable HCC who were ineligible for any locoregional therapy, IMbrave150 recruited patients with locally advanced or metastatic and/or unresectable HCC. “This means that we now consider fit for systemic therapies patients at a slightly earlier stage in the patient journey—in other words patients who are fit for any kind of therapy without having a very grim prognosis,” Sangro said.

In the study, patients were randomized 2:1 to receive atezolizumab at 1200 mg plus bevacizumab at 15 mg/kg every 3 weeks or sorafenib at 400 mg twice a day. The primary end points were OS and progression-free survival (PFS) per RECIST 1.1 criteria by independent review.

Sangro noted that the efficacy of the combination regimen was maintained in updated findings from IMbrave150 reported at the 2021 Gastrointestinal Cancers Symposium. The median OS was 19.2 months (95% CI, 17.0-23.7) among 336 patients who received atezolizumab plus bevacizumab compared with 13.4 months (95% CI, 11.4-16.9) among 165 participants who took sorafenib (HR, 0.66; 95% CI, 0.52-0.85; \( P = .0009 \)). The median PFS was 6.9 months (95% CI, 5.7-8.6) with atezolizumab/bevacizumab vs 4.3 months (95% CI, 4.0-5.6) with sorafenib (HR, 0.65; 95% CI, 0.53-0.81; \( P = .0001 \)).

After a median follow-up of 15.6 months, the confirmed objective response rate (ORR) by RECIST 1.1 criteria among patients with measurable disease at baseline who received atezolizumab/bevacizumab (n = 326) was 30% (95% CI, 25%-35%), including a complete response (CR) rate of 8%. Among those treated with sorafenib (n = 159), the confirmed ORR was 11% (95% CI, 7%-17%), including a CR rate of less than 1%. Moreover, the median duration of response was 18.1 months (95% CI, 14.6-NE) with atezolizumab/bevacizumab vs 14.9 months (95% CI, 4.9-17.0) with sorafenib.

Updated exploratory subgroup analyses also showed a trend for improved OS and PFS with the atezolizumab/bevacizumab combination compared with sorafenib regardless of etiology. The hazard ratios for median OS and median PFS favored the combination for patients with hepatitis B virus (0.56 and 0.51, respectively) and for participants with hepatitis C (0.43 and 0.68, respectively). For nonviral HCC, the combination was less effective than sorafenib for median OS (HR, 1.05) with a lower median PFS benefit (HR, 0.80).\(^6\)

Of note, IMbrave150 recruited patients with high-risk features who had been excluded from previous trials, Sangro said. In an updated analysis of the intention-to-treat population (N = 501), patients with high-risk status comprised 19% of those enrolled in the atezolizumab/bevacizumab arm and 22% of participants in the sorafenib arm. Patients with portal vein thrombosis made up 53% and 54% of the investigational and comparative arms, respectively, including 14% and 15% with a tumor thrombosis in the main trunk and/or contralateral portal vein classified as portal vein tumor thrombosis stage Vp4.\(^11,12\)

In updated data, the atezolizumab/bevacizumab combination resulted in a similar OS benefit compared with sorafenib for patients with high-risk features (HR, 0.62) as it did for those without high-risk features (HR, 0.68).\(^12\)

Overall, Sangro said, the atezolizumab/bevacizumab combination is a good option for patients with high-risk disease. However, he noted that the risk of esophageal varices and bleeding is an underlying factor with chronic HCC due to portal hypertension. In IMbrave150, patients with Vp4 disease had higher rates of bleeding events with atezolizumab/bevacizumab compared with sorafenib, including for esophageal varices hemorrhage (14% vs 0%) and upper gastrointestinal hemorrhage (7% vs 0%).\(^11\)

“Patients considered for atezolizumab-/bevacizumab as a first-line systemic option should undergo esophageal varices screening with endoscopy and, if varices are present, particularly if they are large, they should be treated as per standard of care in the institutions,” Sangro said.

**ADDITIONAL LATE-STAGE FINDINGS**

**Sintilimab Combination**

Since June 2021, investigators have been reporting positive findings from several

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### TABLE. Select Phase 3 Trials of First-Line Immunotheay Combinations in HCC\(^a\)

<table>
<thead>
<tr>
<th>Study name (ClinicalTrials.gov identifier)</th>
<th>Description</th>
<th>Estimated enrollment/primary completion date</th>
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</table>

**HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor.**

\(^a\)These are global phase 3 trials. Additional phase 3 trials are being conducted in China.

\(^b\)Trial is active but no longer recruiting participants.

\(^c\)Lenvatinib is dosed according to body weight: 8 mg < 60 kg and 12 mg ≥ 60 kg.

\(^d\)Tremelimumab is tested in 2 combination arms at a single 300-mg priming dose or at 75 mg for 4 doses.
other late-stage studies of novel therapies in unresectable HCC.

The combination of sintilimab, an anti-PD-1 inhibitor, plus IBI305, a bevacizumab biosimilar, was tested against single-agent sorafenib as first-line therapy for patients with unresectable HCC with hepatitis B virus infection in the phase 2/3 ORIENT-32 study (NCT03794440). The study, which enrolled 595 patients, was conducted in China.

After a median follow-up of 10.0 months, patients who received the combination had a median PFS of 4.6 months (95% CI, 4.1-5.7) compared with 2.8 months (95% CI, 2.7-3.2) for those who were treated with sorafenib (HR, 0.56; 95% CI, 0.46-0.70; P < .0001). In the first interim analysis, the median OS was not reached (NR) in the combination arm (95% CI, NR-NR) compared with 10.4 months (95% CI, 8.5-NR) in the sorafenib group.4

In June 2021, the National Medical Products Administration of China approved the combination as first-line treatment for patients with advanced or unresectable HCC based on the ORIENT-32 findings, according to Innovent Biologics, Inc, a Chinese company collaborating with Eli Lilly and Company to develop the drug.

Chinese regulators also have approved sintilimab, which is marketed in China under the trade name Tyvyt, for classical Hodgkin lymphoma and non–small cell lung cancer (NSCLC) settings. IBI305, known as Byvasda, carries indications for metastatic colorectal cancer, adult recurrent glioblastoma, and advanced NSCLC.13 Meanwhile, the FDA is reviewing a biologics license application for the use of sintilimab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of patients with nonsquamous NSCLC, according to Innovent and Lilly.14

**Cabozantinib Regimen**

Another regimen yielding positive PFS data combines atezolizumab with cabozantinib (Cabometyx), which was tested against cabozantinib monotherapy and single-agent sorafenib in patients with previously untreated advanced HCC in the phase 3 COSMIC-312 trial (NCT03755791). Cabozantinib, which inhibits multiple TKs including several involved in tumor angiogenesis, is approved for patients with HCC who have been previously treated with sorafenib.15

Findings from a planned primary analysis demonstrate that the combination reduced the risk of disease progression or death by 37% compared with sorafenib (HR, 0.63; 99% CI, 0.44-0.91; P = .0012), according to a joint press release from Exelixis, Inc, and Ipsen, the companies developing the regimen. Although there was a trend toward improved OS, the benefit was not statistically significant and the likelihood of reaching that benchmark is low, the companies said. A final OS analysis is expected in early 2022.16

The findings may have been affected by factors including patient demographics, subsequent anticancer therapy, and the impact of the COVID-19 pandemic on the trial, Michael M. Morrissey, PhD, Exelixis’ president and CEO, said in the press release. The company plans to discuss next steps for a potential regulatory filing with the FDA.16

**Donafenib Monotherapy**

In another study conducted in China, investigators report that donafenib, a modified form of sorafenib, demonstrated superior OS outcomes compared with sorafenib in a phase 2/3 trial involving patients with unresectable or metastatic HCC who had not received prior systemic therapy.

In the full analysis set of 659 patients, the median OS was 12.1 months (95% CI, 10.2-13.4) among the 328 participants treated with donafenib compared with 10.3 months (95% CI, 9.2-12.0) for the 331 patients who received sorafenib (HR, 0.831; 95% CI, 0.699-0.988; P = .0245). The confirmed ORR was 4.6% with donafenib vs 2.7% with sorafenib.

The findings make donafenib the only monotherapy to demonstrate superiority over sorafenib for this patient population, resulting in a new first-line option for patients in China, investigators said.5

**FUTURE DIRECTIONS**

The prospect of new frontline options for patients with unresectable HCC raises numerous clinical questions. During the ILCA 2021 presentation, attendees asked whether clinical trials that use sorafenib as a comparator are outmoded in light of recent data.

Lorenza Rimassa, MD, who presented a case-based discussion of the atezolizumab/bevacizumab combination during the presentation, said most ongoing trials are comparing novel therapies with sorafenib or lenvatinib. “We probably will never have a direct comparison” of novel regimens, said Rimassa, an associate professor of medical oncology at Humanitas University and head of gastrointestinal oncology at Humanitas Cancer Center, Humanitas Research Hospital-IRCSS (Scientific Institute for Research, Hospitalization and Healthcare) in Milan, Italy.

She said clinicians would have to compare novel regimens through indirect comparisons such as meta-analyses and other statistical approaches.

“If these trials are positive and eventually all the combinations get approved, and then reimbursed and so available for us as physicians, we will have to choose,” Sangro said. “Of course, safety issues will be an important point when you have to decide what to use, what combination to use, what treatment to use.”

Second-line therapy is another area with a growing menu of choices but sparse data to guide recommendations.

Overall, Sangro noted that IO combination therapy might not be appropriate for subgroups of patients with contraindications for immunotherapy such as those who need immunosuppressive therapy or have autoimmune conditions. Similarly, some patients have contraindications for antiangiogenics such as recent cardiac events or thrombosis.

“At the end of the day, we will have a very interesting time,” Sangro said. “We really need to share opinions so that we can all together make wise decisions and recommendations,” he said.

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**This presentation was part of the Industry Symposia at ILCA 2021 and was sponsored by Roche, which is developing atezolizumab through Genentech, a member of the Roche Group.**

For a full list of references, see the article at OneLive.com.
IN THE TREATMENT OF **RELAPSED REFRACTORY MULTIPLE MYELOMA** IN COMBINATION WITH **POMALIDOMIDE AND DEXAMETHASONE (Pd)**

**ACHIEVE GREATER OUTCOMES FOR YOUR PATIENTS**

SARCLISA is an anti-CD38 therapy proven to deliver **superior PFS** (median PFS of 11.53 months with **SARCLISA + Pd** vs 6.47 months with **Pd alone**), **HR=0.596, 95% CI: 0.44, 0.81, P=0.0010**). SARCLISA also demonstrated a **significant increase in ORR** (60.4% with **SARCLISA + Pd** [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)*

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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)**

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®)

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.¹ CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; NCCN=National Comprehensive Cancer Network; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

**Indication**

SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

**Important Safety Information**

**CONTRAINDICATIONS**

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

**WARNINGS AND PRECAUTIONS**

**Infusion-Related Reactions**

Infusion-related reactions (IRRs) have been observed in 39% of patients treated with SARCLISA. All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an IRR included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Choose SARCLISA + Pd to Offer Improved Outcomes to More Patients vs Pd Alone

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Studied in the phase 3 ICARIA-MM trial, which included patients with poor prognostic factors

Based on the ICARIA-MM trial, SARCLISA + Pd is a treatment choice for patients with relapsed refractory multiple myeloma

- Who have received at least 2 prior therapies, including lenalidomide and a PI
- Who may have renal impairment (creatinine clearance <60 mL/min/1.73 m²), high cytogenetic risk, or a history of COPD or asthma
- Who may have poor performance status or are ≥75 years of age
- Who are refractory to lenalidomide, a PI, or both

**STUDY DESIGN:** ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint; ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.

**PATIENT CHARACTERISTICS:** The median patient age was 67 years (range, 36 to 86), and 20% of patients were ≥75 years of age. Ten percent of patients entered the study with a history of COPD or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 34%. The ISS stage at study entry was I in 37%, II in 36%, and III in 25% of patients. Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14), and t(14;16) were present in 12%, 8%, and 2% of patients, respectively. The median number of prior lines of therapy was 3 (range, 2 to 11). All patients received a prior PI, all patients received prior stem cell transplantation; the majority of patients (93%) were refractory to lenalidomide, 76% to a PI, and 73% to both an immunomodulator and a PI.

COPD=chronic obstructive pulmonary disease; ISS=International Staging System; IV=intravenous; OS=overall survival; PI=proteasome inhibitor.

**Important Safety Information (cont’d)**

**Infusion-Related Reactions (cont’d)**

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.
SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone\(^1\)

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd.\(^1\)

At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.\(^1\)

SARCLISA + Pd showed a significant increase in ORR\(^1\)*

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60.4%</strong> ORR</td>
<td><strong>35.3%</strong> ORR</td>
</tr>
<tr>
<td>(P&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td><strong>31.8%</strong> ≥VGPR</td>
<td><strong>8.5%</strong> ≥VGPR</td>
</tr>
<tr>
<td>~4\times increase</td>
<td></td>
</tr>
<tr>
<td><strong>35</strong> days</td>
<td><strong>58</strong> days</td>
</tr>
<tr>
<td>Median time to first response among responders</td>
<td>Median time to first response among responders</td>
</tr>
</tbody>
</table>

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

Important Safety Information (cont’d)

**Neutropenia**

SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Important Safety Information (cont’d)

Neutropenia (cont’d)
Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies
Second primary malignancies were reported in 3.9% of patients in the SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm), and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies.

Laboratory Test Interference
**Interference with Serological Testing (Indirect Antiglobulin Test)**
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA–multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

**Interference with Serum Protein Electrophoresis and Immunofixation Tests**
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were neutropenia (laboratory abnormality, 96% Isa-Pd vs 92% Pd), infusion-related reactions (38% Isa-Pd vs 0% Pd), pneumonia (31% Isa-Pd vs 23% Pd), upper respiratory tract infection (57% Isa-Pd vs 42% Pd), and diarrhea (26% with Isa-Pd vs 19% Pd). Serious adverse reactions occurred in 62% of patients receiving SARCLISA. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

USE IN SPECIAL POPULATIONS
Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see accompanying brief summary of full Prescribing Information.


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SARCLISA® Rx Only (isatuximab-irfc) injection, for intravenous use

Brief Summary of Prescribing Information

1 INTRODUCTION TO SARCLISA
SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior lines of therapy including lenalidomide and a proteasome inhibitor.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Administer the following predefined schedule of SARCLISA, pomalidomide, and dexamethasone. Sarclisa is used in combination with pomalidomide and dexamethasone.

Misused SARCLISA Doses

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.2 Recommended Premedications

Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions (see Warnings and Precautions (5.5)).

- Diphenhydramine 25 mg to 50 mg orally or intravenously
- H2 antagonists.
- Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age).
- Acetaminophen 650 mg to 1000 mg orally (or equivalent);
- H2 antagonists.
- Diphendramine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backbone treatment, before SARCLISA and pomalidomide administration.

Administer the following premedications 15 to 60 minutes prior to starting a SARCLISA infusion.

2.3 Dose Modifications

No dose reduction of SARCLISA is recommended. Dose delay may be required if the recovery of blood counts is delayed by the occurrence of hematological toxicity (see Warnings and Precautions (5.5)). For information concerning drugs given in combination with SARCLISA, see manufacturer's prescribing information. For other medical products that are administered with SARCLISA, refer to the respective current prescribing information.

2.4 Preparation

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) (see Dosage and Administration (2.1)). More than one SARCLISA vial may be necessary to obtain the required dose for the patient.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA injection.
- Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to achieve the appropriate SARCLISA concentration for infusion.
- The infusion bag must be made of polyethylene (PE), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag.

2.5 Administration

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadine [PBD], or polyurethane [PUI]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will allow completion of the infusion (see Table 2). Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C–8°C, followed by 6 hours (including the infusion time) at room temperature.
- Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.

Infusion Rates

Following infusion, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only for patients with adverse reactions (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)).

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Days</th>
<th>Initial Rate</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>1, 8, 15, and 22 (weekly)</td>
<td>25 mL/hour for 60 minutes</td>
<td>50 mL/hour by 30 minutes</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
<td>50 mL/hour for 30 minutes</td>
<td>75 mL/hour by 30 minutes</td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients (see Warnings and Precautions (5.1)).

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-related Reactions

Infusion-related reactions have been observed in 39% of patients treated with SARCLISA (see Adverse Reactions (6.1)). All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 98% of cases. The median time to resolution of infusion-related reactions was 4 hours (range, 0–24 hours). In approximately 9% of patients, infusion-related reactions were severe and required medical intervention.

5.2 Neutropenia

Neutropenia may cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal harm when administered to a pregnant woman because pomalidomide may cause fetal death and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-related Reactions (see Warnings and Precautions (5.1)).

6.2 Postmarketing Experience

Serious and potentially fatal adverse reactions, including death, have been reported during postmarketing use of SARCLISA. These reactions have been reported at any time during therapy, including the postmarketing period.

6.3 Adverse Reactions by System Organ Class

The most common adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (7%). Fatal adverse reactions occurred in 11% of patients (7%). Serious adverse reactions included infections (36%), neutropenia (35%), and hematologic adverse reactions (35%). The most common serious adverse reactions included infections, neutropenia, and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

6.4 Laboratory Test Abnormalities

The following represents a postmarketing collection of adverse reactions reported during postmarketing use of SARCLISA. The frequency represents the proportion of patients who experienced at least one adverse event of a specific type.

6.5 Other Information

5.5 Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.3)).

The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause fetal death and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

6.6 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.

6.7 Pregnancy

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/mm³, absolute neutrophil count ≥1.5×10⁹/l, creatinine clearance ≥80 ml/min (MDRD formula), and AST and/or ALT ≤3 × ULN. Patients received SARCLISA 10 mg/kg intravenously weekly. The median age of patients who received Isa-Pd was 68 years (range 39–83); 58% male, 76% white, and 14% Asian. Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions occurred in 5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% were pneumonia and other infections (3%)).

Permanent discontinuation due to an adverse reaction (grades 3–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2%). In addition, SARCLISA and pomalidomide dexamethasone (Isa-Pd) arm and in 0.7% of patients in the Isa-Pd arm) and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of secondary primary malignancies, as per International Myeloma Working Group (IMWG) guidelines.

5.4 Laboratory Test Interference

No laboratory test interference with SARCLISA was observed in practice.
The most common adverse reactions (≥20%) were pneumonia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea. Table 3 summarizes the adverse reactions in ICARIA-MM.

Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>38 (25.0)</td>
<td>1.3 (1.3)</td>
</tr>
<tr>
<td>Infusion-related</td>
<td>57 (37.3)</td>
<td>9 (9.0)</td>
</tr>
<tr>
<td>Infections</td>
<td>26 (17.1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (9.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12 (7.9)</td>
<td>1.3 (1.3)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>17 (11.2)</td>
<td>5.0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>127 (84)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>26 (17.1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (9.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (7.9)</td>
<td>1.3 (1.3)</td>
</tr>
</tbody>
</table>

CTCAE version 4.03

*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jiroveci pneumonia.

†Upper respiratory tract infection includes bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenzae virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

‡Dyspnea includes dyspnea, dyspnea exertional, and dyspnea infusional.

Table 4 summarizes the hematologic laboratory abnormalities in ICARIA-MM.

Table 4: Treatment Emergent Hematologic Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment – ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter (%)</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>15 (9.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (9.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>14 (9.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22 (14)</td>
<td>14 (9)</td>
</tr>
</tbody>
</table>

The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy. Pomalidomide is only available through a REMS program. Clinical Considerations

Fetal/neonatal reactions

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause placentation of fetal CD38-positive immune cells and decreased bone density. Refer to the pomalidomide prescribing information for additional information.

8.2 Lactation

Risk Summary

There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Females

SARCLISA can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)). Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 53% (306 patients) were 65 or over, while 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years of age and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

There is no known specific antidote for SARCLISA overdose. In the event of overdose of SARCLISA, refer to the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.
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**OncLive®** is honored to announce the 2021 Giants of the Cancer Care® inductees. The 14 winners are innovators of change whose invaluable contributions to the field have changed the trajectory of care across tumor types and improved the quality of life for countless patients.

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**BREAST CANCER**

Nancy E. Davidson, MD  
Fred Hutchinson Cancer Research Center/University of Washington School of Medicine/Seattle Cancer Care Alliance

- Davidson was among the first investigators to elucidate the role of apoptosis in the response of human breast cancer cells to estrogen deprivation and certain cytotoxic chemotherapies, demonstrating that these therapies are both antiproliferative and proapoptotic.
- Her research also demonstrated the feasibility of targeting the polyamine metabolic pathway in breast cancer cells, which inhibits proliferation, promotes apoptosis, and downregulates expression of critical molecules such as the estrogen receptor $\alpha$ protein.
- Davidson has led clinical trials involving chemotherapy and endocrine-related therapies for treating premenopausal breast cancer and has increased the understanding of the potential of angiogenesis inhibitors such as bevacizumab (Avastin) for treating metastatic breast cancer.
- She is senior vice president, director, and professor in the Clinical Research Division, as well as the Raisbeck Endowed Chair for Collaborative Research at Fred Hutchinson Cancer Research Center. Davidson also serves as head of the Department of Medicine at the University of Washington School of Medicine.
- Davidson has won the American Society of Clinical Oncology (ASCO) Gianni Bonadonna Breast Cancer Award, ASCO Allen S. Lichter Visionary Leader Award and Lecture, National Cancer Institute Rosalind E. Franklin Award, and she served as president of ASCO (2007-2008) and president of the American Association for Cancer Research (2015-2016).

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**COMMUNITY OUTREACH**

Julie R. Gralow, MD  
Fred Hutchinson Cancer Research Center/University of Washington (UW) School of Medicine/Seattle Cancer Care Alliance

- Gralow is the chief medical officer and executive vice president of the American Society of Clinical Oncology. She is also the Jill Bennett Endowed Professor of Breast Medical Oncology (emeritus) and professor of global health at the UW School of Medicine and director of breast medical oncology at the Seattle Cancer Care Alliance.
- Gralow is cosecretariat for the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries.
- As a result of her work in cancer survivorship in the Ukraine in the 1990s, Gralow founded the Women’s Empowerment Cancer Advocacy Network (WE CAN). She is also cofounder of Team Survivor Northwest, an exercise and fitness program for women survivors of cancer.
- Gralow’s extensive research into bone health during cancer care led to the National Comprehensive Cancer Network convening a multidisciplinary Bone Health in Cancer Care Task Force, helping to establish the role of bisphosphonates in preventing cancer treatment–induced bone loss.
- Gralow is the principal investigator for the clinical core of the Fred Hutchinson Cancer Research Center/UW Breast Cancer Specialized Programs of Research Excellence grant.

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PHOTO CREDIT: TORI SOPER
• Haller is the cochair of the International Society of Gastrointestinal Oncology (ISGIO) Scientific Advisory Board.
• He was lead author for the Intergroup 0089 trial, still the largest trial of an adjuvant treatment trial for patients with high-risk colon cancer, establishing the treatment regimen of 5-fluorouracil (5-FU), leucovorin, and levamisole for high-risk stage II and III disease.
• Haller was coauthor on the Eastern Cooperative Oncology Group (ECOG) E7283 trial, which helped establish infusional 5-FU plus mitomycin C with radiation as the standard of care in anal cancer.
• He previously served as ECOG Gastrointestinal (GI) Committee chair and cochair of the National Cancer Institute GI Intergroup and as president of ISGIO (2009-2010).
• He held the inaugural Deenie Greitzer Gastrointestinal Medical Oncology Professorship, now the Deenie Greitzer and Daniel G. Haller Associate Professorship, at Perelman School of Medicine from 2015 to 2016.
• Haller has been an editor for over 35 years. His work includes the peer-reviewed journals such as Annals of Internal Medicine, Physician Data Query, and a 10-year term as editor-in-chief of the Journal of Clinical Oncology.
• He is a 2017 recipient of The Ruesch Center for the Cure of Gastrointestinal Cancers at Georgetown Lombardi Comprehensive Cancer Center Luminary Awards in GI Cancers and the 2011 ASCO Special Recognition Award.

Toni K. Choueiri, MD
Dana-Farber Cancer Institute/Brigham and Women’s Hospital/Harvard Medical School

• Choueiri is director of the Lank Center for Genitourinary Oncology and of the Kidney Cancer Center at Dana-Farber Cancer Institute/Brigham and Women’s Hospital. He is also the Jerome and Nancy Kohlberg Chair and professor of medicine at Harvard Medical School.
• His research has led to the approval of several drugs and combinations including cabozantinib (Cabometyx), avelumab (Bavencio), pazopanib (Votrient), and axitinib (Inlyta)-avelumab in advanced renal cell carcinoma (RCC).
• Choueiri led the CheckMate 9ER trial (NCT03141177), the results of which led to the FDA approval of cabozantinib/nivolumab (Opdivo), a combination superior to sunitinib (Sutent) for patients with advanced RCC.
• Along with Daniel Heng, MD, Choueiri established the International Metastatic RCC Database Consortium.
• Choueiri helped develop one of the first liquid biopsy methods that could detect early stages of kidney cancers with high accuracy. The test was nearly 100% accurate when used with blood samples.
• His research into biomarkers has shed light on complex immunogenomics mechanisms contributing to response and therapy resistance
• He was coleader for a multinational study to identify COVID-19 risk factors unique to patients with cancer. The results of the CCC19 study (NCT04354701) showed that patients with cancer and COVID-19 had increased risk for 30-day all-cause mortality.

Robert C. Young, MD
RCY Medicine/Fox Chase Cancer Center

• Young is part of the “Gang of Five,” a group of investigators at the National Cancer Institute who developed the first curative regimens for Hodgkin lymphoma and diffuse aggressive lymphomas, specifically the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) protocol.
• For 18 years, Young served as president and CEO at Fox Chase Cancer Center and then served another 2 years as chancellor. The Robert C. Young MD Chair in Cancer Research at Fox Chase is named in his honor.
• Prior to Fox Chase, he served in various positions at the National Cancer Institute (NCI), including a 14-year term as chief of the medicine branch.
• Young’s research contributed to the standardized staging and grading of ovarian tumors, identified prognostic factors for patients with ovarian cancer, and demonstrated that combination chemotherapy was more effective for patients with advanced ovarian adenocarcinoma vs standard-of-care melphalan.
• Along with Robert F. Ozols, MD, PhD, Young contributed to the understanding of how tumors develop resistance. The pair received the 25th Annual Bristol Myers Squibb Award for Distinguished Achievement in Cancer Research (2002).
• Young is the recipient of several awards including the American Association for Cancer Research Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research (2013) and the American Society of Clinical Oncology Distinguished Service Award for Scientific Leadership (2004).
LUNG CANCER

Pasi A. Jänne, MD, PhD
Dana-Farber Cancer Institute/Harvard Medical School

- Jänne was one of the investigators to aid in the discovery of EGFR mutations and has led the development of therapeutic strategies for patients with EGFR-mutant lung cancer.
- He and his colleagues demonstrated that loss of response to gefitinib (Iressa) was driven by MET amplification, paving the way for further study of resistance mechanisms to earlier- and next-generation inhibitors.
- Jänne was the primary investigator for the phase 1 AURA trial (NCT01802632) that evaluated the efficacy of osimertinib (Tagrisso) in patients with non–small cell lung cancer (NSCLC). The agent is approved as adjuvant therapy following tumor resection in patients with NSCLC with tumors that have EGFR exon 19 deletions or exon 21 L858R mutations.
- Jänne is the director of 3 centers at Dana-Farber Cancer Institute: Lowe Center for Thoracic Oncology, Belfer Center for Applied Cancer Science, and Chen-Huang Center for EGFR-Mutant Lung Cancers.
- He is also a professor of medicine at Harvard Medical School.
- Jänne has received numerous awards including the American Society of Clinical Oncology Science of Oncology Award (2020), the National Cancer Institute Outstanding Investigator Award (2018), the European Society for Medical Oncology Translational Research Award (2018), American Association for Cancer Research Waun Ki Hong Award for Outstanding Achievement in Translational and Clinical Cancer Research (2018).

LYMPHOMA

Steven T. Rosen, MD
City of Hope

- Rosen is provost and chief science officer, director of the Comprehensive Cancer Center, the Irell & Manella Cancer Center Director’s Distinguished Chair, the Morgan & Helen Chu Director’s Chair and director of the Beckman Research Institute, and director of the Irell & Manella Graduate School of Biological Sciences at City of Hope.
- Rosen was previously director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University for 24 years. The National Cancer Institute (NCI) named Lurie an NCI-designated comprehensive cancer center under Rosen’s leadership.
- Rosen is a pioneer in the development monoclonal antibodies and recombinant toxins that can specifically target cancer cells.
- He led pivotal research into apoptosis inducers, proteasome inhibitors, and metabolism inhibitors as methods to promote cancer cell death. His research also led to the discovery that RNA-based analogs and cell signaling regulators can interfere with cancer growth processes.
- Rosen has been a leader of investigations to the discovery of how interferons and cytokines can trigger an immune response against cancer cells and angiogenesis inhibitors to prevent cancer cells from growing new blood vessels.
- He has been at the forefront of research into hormone therapies and transcriptional regulators and antisense compounds to activate or silence certain genes in cancer and normal cells.

MELANOMA

Michael B. Atkins, MD
Georgetown Lombardi Comprehensive Cancer Center/ MedStar Georgetown University Hospital

- Atkins is a pioneer in the introduction of immunotherapy for the treatment of cancer and one of the world’s leading authorities in cancer immunotherapy.
- His research helped establish dual checkpoint blockade with antibodies against both PD-1 and CTLA-4 as the standard of care in melanoma. The nivolumab (Opdivo)/ipilimumab (Yervoy) combination induces extended treatment-free melanoma remissions in more than 50% of patients.
- He was a founding member and leader of the Cytokine Working Group and leader of the Georgetown Lombardi Cancer Immunotherapy Interest Group.
- Atkins has led several major multi-investigator clinical and translational research efforts. His research in melanoma and kidney cancer has uncovered critical biology of these diseases and led to FDA approval of more than 20 new treatments.
- Atkins established and led the cutaneous and biologic therapy programs at Beth Israel Deaconess Cancer Center and codeveloped a new staging system for melanoma.
- He is deputy director of the Georgetown Lombardi Comprehensive Cancer Center, the William M. Scholl Professor and vice chair of the Department of Medical Oncology at Georgetown University Medical Center, and codirector of the Melanoma Research Program at MedStar Georgetown University Hospital.
- He has published more than 500 scientific and review articles, coedited 5 books, and given more than 700 lectures worldwide.
- Atkins served as president of the Society for Immunotherapy of Cancer from 2002 to 2004.

MYELOMA

Paul G. Richardson, MD
Dana-Farber Cancer Institute/Harvard Medical School

- Richardson is the clinical program leader and director of clinical research at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute and the RJ Corman Professor of Medicine at Harvard Medical School.
- During a career that has spanned more than 25 years, Richardson has contributed to the development of 3 major classes of therapies that have transformed the treatment of patients with multiple myeloma.
- He led or co-led the clinical development and study of immunomodulatory drugs thalidomide (Thalomid), lenalidomide (Revlimid), and pomalidomide (Pomalyst); proteasome inhibitors bortezomib (Velcade) and ixazomib (Ninlaro); and monoclonal antibodies daratumumab (Darzalex) and elotuzumab (Empliciti).
- Richardson’s groundbreaking clinical work on lenalidomide helped pave the way for FDA approval of the drug in 2006. He was the principal investigator for the landmark SUMMIT trial of bortezomib in relapsed/refractory myeloma, which led the FDA to grant accelerated approval for the drug in just 3 years, and later led the APEX trial (NCT00048230), which resulted in the FDA granting full approval to bortezomib.
- He also played a pivotal role in the phase 3 PANORAMA1 trial, which led to FDA approval of panobinostat (Farydak) combination with bortezomib and dexamethasone for patients with previously treated myeloma.
**PEDIATRICS**

Richard J. O'Reilly, MD  
Memorial Sloan Kettering Cancer Center (MSK)

- O'Reilly and his colleagues developed and introduced methods for removing T cells from a donor's transplant, allowing use of matched unrelated donors for bone marrow transplants and T-cell–depleted transplants from human leukocyte antigen half-matched donors without the risk of graft-vs-host disease.
- He developed new immune cell therapies to manage other potential complications of transplantation, such as Epstein-Barr virus–associated lymphomas and cytomegalovirus infections.
- In 1973, O'Reilly participated in the first transplant of bone marrow from an unrelated donor to a patient.
- O'Reilly founded the clinical and preclinical research program at MSK and established a worldwide reputation for bone marrow transplantations in children with severe combined immune deficiencies and leukemias.
- He serves as the Claire L. Tow Chair for Pediatric Oncology Research at MSK.
- O'Reilly was the 2016 inaugural recipient of the Society of Memorial Sloan Kettering Prize, which honors individuals who have made outstanding contributions to the field of pediatric oncology.
- He has been honored with several awards throughout his career including the Lauri Strauss Leukemia Foundation Timothy Gee Humanity in Medicine Award (2011), the Pediatric Blood and Marrow Transplant Consortium Lifetime Achievement Award (2011), the Society for Translational Oncology Pinedo Cancer Care Prize (2009), and the Leiden University Boerhaave Medal (2000).

**PREVENTION/GENETICS**

Matthew L. Meyerson, MD, PhD  
Dana-Farber Cancer Institute/Harvard Medical School

- Meyerson’s laboratory developed the use of single nucleotide polymorphism arrays for human cancer genome analysis and defined both lineage-specific and cancer-universal regions of amplification and deletion.
- He identified the most common DNA amplification in lung adenocarcinoma, common SOX2 amplification in squamous cell carcinomas, and amplification of antiapoptotic genes including MCL1 across multiple human cancers.
- His research contributed to the identification of mutations in the EGFR gene in lung adenocarcinomas as well as activating mutations of FGFR2 in multiple cancers and ALK mutations in glioblastoma.
- Meyerson pioneered the use of single-template sequencing in cancer genome analysis and discovered genetic mutations associated with breast, colon, and lung cancers.
- He developed a genomic approach to discover microbial sequences in human disease that has been applied to cancers and inflammatory and autoimmune diseases. He completed a new software approach for identifying pathogens using next-generation sequencing data.
- Meyerson is a professor of genetics and pathology at Harvard Medical School and director of the Center for Cancer Genomics at Dana-Farber Cancer Institute.

**RADIATION ONCOLOGY**

Walter J. Curran Jr, MD  
GenesisCare

- Curran is the Global Chief Medical Officer of GenesisCare. He previously served as executive director of Winship Cancer Institute of Emory University and is professor emeritus and former chairman of the Department of Radiation Oncology at Emory University School of Medicine. He was also a group chairman and principal investigator of NRG Oncology.
- Curran was named a Georgia Research Alliance Eminent Scholar and Chair in Cancer Research (2013).
- In 2015, former President Jimmy Carter selected Curran as one of the physicians to treat him after he received a diagnosis of multiple myeloma.
- Curran is an international expert in the treatment of patients with locally advanced lung cancer and malignant brain tumors and led landmark clinical and translational trials in both areas. He is responsible for defining a universally adopted staging system for patients with malignant glioma.
- In 2006, a peer survey in *Journal of Medical Imaging* named him the leading radiation oncologist/cancer investigator.
- In 2004, the European Society for Radiotherapy and Oncology named him an honorary member, a position awarded to those who have made a significant contribution to the achievement of the society’s goals, particularly in the field of interdisciplinary or international cooperation.
- Curran was awarded the American Society for Radiation Oncology Gold Medal (2019) and the Brain Tumor Foundation for Children Visionary Award (2012).

**SUPPORTIVE, PALLIATIVE, AND/OR GERIATRIC CARE**

Dawn L. Hershman, MD, MS  
Herbert Irving Comprehensive Cancer Center at Columbia University

- Hershman has developed a comprehensive multidisciplinary program to study how to improve cancer care delivery, which includes reducing disparities and designing studies to improve the quality of life and quality of care for survivors.
- Her seminal 2018 paper, “Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer” demonstrated that acupuncture significantly improved pain scores in from baseline to 6 weeks.
- Hershman is vice chair of the Southwestern Oncology Group/National Cancer Institute Community Oncology Research Program research base and cochair of the Cancer Care Delivery Committee.
- She is the director of breast oncology and coleader of the Cancer Population Science Program at Columbia University Herbert Irving Comprehensive Cancer Center.
- Previous awards include the Columbia University Irving Medical Center and Irving Institute for Clinical and Translational Research Mentor of the Year Award (2021), the Hologic Inc Endowed Women Who Conquer Cancer Mentorship Award (2020), the American Society of Clinical Oncology Advanced Clinical Research Award in Breast Cancer (2010), and the Conquer Cancer Career Development Award (2002).
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To decrease the incidence of chemotherapy-induced myelosuppression in patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

**SPARE THE MARROW. COSELA HELPS PROTECT AGAINST MYELOSUPPRESSION,**

**INDICATION**

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

*Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

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PReCOSELA vs without COSELA

The Pivotal Study (Study 1) compared an etoposide/carboplatin + atezolizumab (E/P/A) regimen with COSELA in 107 patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. In this study, COSELA significantly reduced the incidence of Grade 3/4 anemia was 19% and 28% (aRR 0.663 [95% CI, 0.336, 1.310]) and RBC transfusions on/after 5 weeks were 13% and 21% (aRR 0.642 [95% CI, 0.294, 1.404]) with COSELA compared with without COSELA.

The incidence of Grade 3/4 anemia was 19% and 28% (aRR 0.663 [95% CI, 0.336, 1.310]) and RBC transfusions on/after 5 weeks were 13% and 21% (aRR 0.642 [95% CI, 0.294, 1.404]) with COSELA compared with without COSELA.

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The Pivotal Study (Study 1) compared an etoposide/carboplatin + atezolizumab (E/P/A) regimen with COSELA vs without COSELA.

**TRILACICLIB IS A RECOMMENDED PROPHYLACTIC OPTION FOR CERTAIN PATIENTS WITH ES-SCLC BY THE NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®)**

**PROACTIVELY HELP PROTECT AGAINST MULTIPLE MYELOSUPPRESSIVE CONSEQUENCES WITH THE FIRST AND ONLY MYELOPROTECTION THERAPY**

Visit COSELA.com for more details.

**COSELA™ (trilaciclib) helps protect hematopoietic stem and progenitor cells (HSPCs), the source of blood cell lineages**

**WARNINGS AND PRECAUTIONS**

COSELA administration can cause injection-site reactions, including phlebitis and thrombophlebitis, which occurred in 56 (21%) of 272 patients receiving COSELA in clinical trials, including Grade 2 reactions (2%). Monitor patients for signs and symptoms of acute drug hypersensitivity to trilaciclib.

COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib.

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

Embryo-Fetal Toxicity

Based on its mechanism of action, COSELA can cause fetal harm when administered during pregnancy. Women of reproductive potential and men who have sexual contact with pregnant women should use effective contraception during treatment with COSELA and for at least 3 weeks after the final dose.

COSELA is contraindicated in patients with a history of severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis.

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinase (CDK) inhibitors. If a patient develops recurrent Grade 2 ILD/pneumonitis, or severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

If a patient develops recurrent Grade 2 ILD/pneumonitis, or severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-G1TX or www.g1therapeutics.com. Reference: COSELA (trilaciclib). Prescribing Information. G1 Therapeutics, Inc; 02/2021.
**SPEAR THE TUMOR.**
**WHILE CHEMOTHERAPY TARGETS CANCER CELLS**

**SELECT IMPORTANT SAFETY INFORMATION**

**CONTRAINICATION**
- COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib.

**WARNINGS AND PRECAUTIONS**

**Injection-Site Reactions, Including Phlebitis and Thrombophlebitis**
- COSELA administration can cause injection-site reactions, including phlebitis and thrombophlebitis, which occurred in 56 (21%) of 272 patients receiving COSELA in clinical trials, including Grade 2 (10%) and Grade 3 (0.4%) adverse reactions. Monitor patients for signs and symptoms of injection-site reactions, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue COSELA. Injection-site reactions led to discontinuation of treatment in 3 (1%) of the 272 patients.

**Acute Drug Hypersensitivity Reactions**
- COSELA administration can cause acute drug hypersensitivity reactions, which occurred in 16 (6%) of 272 patients receiving COSELA in clinical trials, including Grade 2 reactions (2%). Monitor patients for signs and symptoms of acute drug hypersensitivity reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold COSELA until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue COSELA.

**Interstitial Lung Disease/Pneumonitis**
- Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, including COSELA, with which it occurred in 1 (0.4%) of 272 patients receiving COSELA in clinical trials. Monitor patients for pulmonary symptoms of ILD/pneumonitis. For recurrent moderate (Grade 2) ILD/pneumonitis, and severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

**Embryo-Fetal Toxicity**
- Based on its mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use an effective method of contraception during treatment with COSELA and for at least 3 weeks after the final dose.

**ADVERSE REACTIONS**
- The most common adverse reactions (≥10%) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia.

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To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-G1TX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This information is not comprehensive. Please see the Brief Summary of Prescribing Information on the adjacent page.
COSELA™ (trilaciclib) for injection, for intravenous use

Initial U.S. Approval: 2021

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients who are scheduled to receive high-dose platinum-containing regimens or hematopoietic cell transplantation regimens for extensive-stage small cell lung cancer (ES-SCLC).

DOSE AND ADMINISTRATION

Recommended Dose

The recommended dose of COSELA is 240 mg/m² per day. Administer as a 30-minute intravenous infusion at least 4 hours prior to the start of chemotherapy on each day chemotherapy is administered. The interval between doses of COSELA on sequential days should not be greater than 28 hours. 

Injection site reactions, including phlebitis and thrombophlebitis

Injection site reactions, including phlebitis and thrombophlebitis, occurred in 56 (21%) of 272 patients who received COSELA. The most common adverse reactions (≥10%) were: Grade 1: hypocalcemia, hypokalemia, and thrombosis.

Table 1: Recommended Actions for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severi ty Grade*</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions, including phlebitis and thrombophlebitis</td>
<td>3 (1%)</td>
<td>Flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, permanently discontinue COSELA (see Dosage and Administration (2.2)).</td>
</tr>
</tbody>
</table>

CONTRAINdications

Severe, life-threatening, or fatal intestinal disease (ILD) and/or pneumonitis can occur in patients given COSELA. 

WARNINGS AND PRECAUTIONS

Intestinal lung disease or pneumonitis

Seventy-one percent of patients receiving COSELA and 78% of patients receiving placebo completed at least 4 cycles of therapy. The median duration of treatment was 6 cycles in each treatment group. 

Table 2: COSELA Prior to Topotecan

<table>
<thead>
<tr>
<th>Study</th>
<th>Study ID (NCT#)</th>
<th>Study Design</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>NCT03413113</td>
<td>Randomized, double-blind, placebo-controlled trial of COSELA prior to topotecan for patients with ES-SCLC previously treated with platinum and etoposide (EP) for patients with newly diagnosed ES-SCLC not previously treated with chemotherapy.</td>
<td>Thirty-eight percent of patients receiving COSELA and 29% of patients receiving placebo completed 5 or more cycles of therapy. The median duration of treatment was 3 cycles in each treatment group.</td>
</tr>
<tr>
<td>Study 2</td>
<td>NCT01285397</td>
<td>Randomized, double-blind, placebo-controlled study of COSELA or placebo administered prior to treatment with topotecan for patients with ES-SCLC.</td>
<td>The most common adverse reactions (≥10%) were: Grade 1: hypocalcemia, hypokalemia, and thrombosis.</td>
</tr>
</tbody>
</table>

Interruption in Treatment

The following clinically significant adverse reactions are described elsewhere in the label: Grade 3: treatment-emergent adverse event (TEAE) preferred terms 'Hypocalcemia,' 'Blood aspartate aminotransferase increased,' 'Blood alanine aminotransferase increased,' 'Blood bilirubin increased,' 'Blood total bilirubin increased,' 'Fatigue,' 'Hypokalemia.' Grade 4: treatment-emergent adverse events 'Hypocalcemia,' treatment-related asthma, and neutropenic sepsis. 

Table 3: Incidence in COSELA Compared to Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>COSELA (N=122)</th>
<th>Placebo (N=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3</td>
<td>All Grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>hypokalemia</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Apparent amiodarone metabolism increased</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Cough</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Hematological</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infusion-related</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Pregnancy

Pregnancy

There are no data on the presence of trilaciclib in either human or animal milk. The benefits of breastfeeding outweigh the potential adverse effects on the infant when COSELA is administered to breastfeeding women. Advise breastfeeding women not to breastfeed while taking COSELA and for at least 3 weeks after the last dose. 

Lactation

Lactation

No studies have been performed in humans to evaluate the effects of COSELA on fertility in either sex. 

Pediatric Use

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. 

Geriatrics

Geriatrics

In the pooled efficacy dataset from Studies 1, 2 and 3, 46% of 123 patients randomized to COSELA were 65 years of age or older. No overall differences in safety or effectiveness of COSELA were observed between these patients and younger patients. 

Hepatic Impairment

Hepatic Impairment

Use of COSELA is not recommended in patients with moderate or severe hepatic impairment. No dosage adjustment is recommended in patients with severe hepatic impairment. 

Drug Interactions

Drug Interactions

Adverse reactions have been observed in patients given COSELA with a 20% increase in drug exposure compared to patients receiving placebo. 

Table 4: Potentially Significant Drug Interactions with COSELA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Mod.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide</td>
<td>The potential benefits of taking COSELA concurrently with dofetilide should be considered</td>
<td>Increased dofetilide levels were observed in patients receiving COSELA.</td>
</tr>
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</table>

USE IN SPECIFIC POPULATIONS

Prognosis

Prognosis

Based on the mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12)). There are no available animal or human data on COSELA use to evaluate for a risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. 

Contraindications

COSELA can cause fetal harm when administered to pregnant women (see Use in Specific Populations (8.2)). Advise female patients of reproductive potential to use effective contraception during treatment with COSELA and for at least 3 weeks after the final dose. 

Pediatric Use

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Safety and effectiveness in pediatric patients have not been established. 

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To prescribe the information for these concomitant medications for assessing the benefit and risk of concurrent use of COSELA. 

Table 4: Potentially Significant Drug Interactions with COSELA

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Important information about COSELA is available at www.COSELA.com.
Continued Efficacy Sets Cilta-Cel As a Viable Treatment Option for Patients With Relapsed/Refractory Myeloma

by COURTNEY MARABELLA

A SINGLE DOSE OF cilta-cabtagene autoleucel (cilta-cel) sustained early, deep, and durable responses and showcased a manageable safety profile in heavily pretreated patients with multiple myeloma, according to updated data from the phase 1b/2 CARTITUDE-1 trial (NCT03548207) presented during the Society of Hematologic Oncology 2021 Annual Meeting.1

At a median follow-up of 18 months, the chimeric antigen receptor (CAR) T-cell therapy elicited an overall response rate (ORR) of 97.9% among 97 patients, with a stringent complete response (sCR) rate of 80.4%. Further, 94.8% of patients had a very good partial response or better and 3.1% had a partial response. Notably, response rates with cilta-cel were comparable across different subgroups examined, including previous lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk.

The updated efficacy data builds on the promising results from CARTITUDE-1 at a median follow-up of 12.4 months. Specifically, the agent induced an ORR of 97%, with a sCR of 67%. The 12-month progression-free survival (PFS) rate was 77% and the 12-month overall survival (OS) rate was 89%.

No new safety signals were reported with longer follow-up. “Successful new patient management strategies implemented in the CARTITUDE program [helped to] prevent and reduce the incidence of neurotoxicity,” said Saad Z. Usmani, MD, the director of the Plasma Cell Disorder program at Levine Cancer Institute, Atrium Health, in a presentation of the data. Usmani is also the director of clinical research in hematologic malignancies at Levine and is a clinical associate professor of medicine at University of North Carolina School of Medicine.

Mitigation strategies employed on this study to reduce the incidence of neurotoxicity included: enhanced bridging therapy to reduce tumor burden; early and aggressive treatment of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS); and extended monitoring, including handwriting assessments.

To be eligible for enrollment, patients had to have a confirmed diagnosis of progressive multiple myeloma, according to International Myeloma Working Group criteria; they also had to have received at least 3 prior therapies or be double refractory. Additionally, patients had to have measurable disease, an ECOG performance status of 0 or 1, and have received prior treatment with proteasome inhibitors, immunomodulatory drugs, or an anti-CD38 therapy.

Participants enrolled to the study underwent 28 days of screening prior to apheresis; this was followed by bridging therapy, as needed (FIGURE).2 Thereafter, patients underwent lymphodepletion with cyclophosphamide at a dose of 300 mg/m² and fludarabine at a dose of 30 mg/m² on days -5 to -3 prior to infusion. On day 1, patients received infusion with cilta-cel at a target dose of 0.75 × 10⁶ (range, 0.5-1.0 × 10⁶) CAR-positive viable T cells/kg. The median administered dose was 0.71 × 10⁶ CAR-positive viable T cells/kg.

Post-infusion assessments were focused on examining safety, efficacy, pharmacokinetics, and pharmacodynamics of the agent, as well as biomarker testing.

The primary end point of the phase 1b portion of the study was to characterize the safety of cilta-cel and determine the recommended phase 2 dose. The primary end point of the phase 2 portion of the trial was...
In total, 113 patients were enrolled and underwent apheresis, 101 went on to receive lymphodepletion, and 97 were treated with cilta-cel. Among those who received the CAR T-cell therapy, 29 patients were enrolled to the phase 1b portion of the study (n = 23 ongoing), and 68 were enrolled to the phase 2 portion (n = 53 ongoing).

Overall, 73 patients received bridging therapy and the median turnaround time for the CAR T-cell therapy was 29 days (range, 23-64). Notably, no patients discontinued because of a manufacturing failure, and just 1 patient received retreatment with cilta-cel.

The median age of patients enrolled to the study was 61.0 years (range, 43-78), 58.8% were male, and 17.5% were Black. Moreover, 13.4% had extramedullary plasmacytomas and 6.2% had bone-based plasmacytomas. Just over 20% (21.9%) had bone-marrow plasma cells that were 60% or higher.

The median number of years since diagnosis was 5.9 (range, 1.6-18.2) and 23.7% of patients had a high-risk cytogenetic profile. Additionally, most patients had tumor BCMA expression of 50% or more (91.9%) and had received 5 or more prior lines of therapy (66.0%). The median number of prior therapies received was 6 (range, 3-18). Notably, 87.6% of patients were triple-class refractory, 42.3% were penta-drug refractory, and 99.0% were refractory to their last line of therapy.

Additional data showed that the median duration of response (DOR) with cilta-cel was 21.8 months (95% CI, 21.8-not estimable [NE]). An estimated 73% of patients did not experience disease progression or death at 12 months, and the median DOR was not reached in those who achieved a sCR. The median time to first response with the CAR T-cell therapy was 1 month (range, 0.9-10.7), and the median time to best response and to a CR or greater was 2.6 months (range, 0.9-15.2).

Among 61 patients evaluable for minimal residual disease (MRD), 91.8% had MRD-negative status at 10-5, compared with 57.7% of all patients (n = 97). In patients with a CR or better, these rates were 89.4% and 43.3%, respectively. The median time to MRD 10-5 negativity was 1 month (range, 0.8-7.7).

The median PFS with cilta-cel was 22.8 months (95% CI, 22.8-NE). Moreover, 18-month PFS rate in all patients was 66.0% (95% CI, 54.9%-75.0%) vs 75.9% (95% CI, 63.6-84.5%) in those who achieved a sCR. The 18-month OS rate in all patients was 80.9% (95% CI, 71.4%-87.6%).

In terms of safety, 94.8% of patients experienced a CRS event; the median time to onset was 7 days (range, 1-12) and the median duration was 4 days (range, 1-97). Most of these cases were grades 1 or 2 in severity (94.6%), and most were resolved within 14 days of onset (98.9%). Additionally, 2.1% of patients experienced ICANS grade 3 or higher, and 9.3% experienced other grade 3 or higher neurotoxicities (TABLE 1). The most frequent grade 3/4 hematologic adverse effects (AEs) experienced with the CAR T-cell therapy included neutropenia (94.8%), anemia (68.0%), and leukopenia (60.8%). The most common non-hematologic grade 3 or higher AEs were hypophosphatemia (7.2%), fatigue (5.2%), and increased aspartate transaminase (5.2%).

"Cilta-cel is being investigated in the ongoing phase 2 CARTITUDE-2 trial [NCT04133636] and the phase 3 CARTITUDE-4 [NCT04181827] trial in earlier-line settings," Usmani said.
IN HER2+ EARLY BREAST CANCER (EBC), UNDERSTAND HER RISK OF RECURRENCE

HER2 = human epidermal growth factor receptor 2.
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.¹

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.¹
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease. This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.

Association between pCR and event-free survival (EFS)* in the HER2+ subgroup analysis of the CTNeoBC study

* EFS was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.

1,989 patients with HER2+ tumors were included in the subgroup analysis. 55% of which did not receive a full year of adjuvant HER2-targeted monotherapy treatment.

While there are different paths you can choose for your patient with HER2+ EBC, her treatment shouldn’t stop at neoadjuvant therapy.
Discover possible adjuvant treatment options that may be right for her*:
For patients who achieve pCR, visit **PCRinEBC.com**
For patients who do not achieve pCR, visit **NoPCRinEBC.com**

*There may be other treatment options available for your patients.

**References:**
Venetoclax Plus FLAG-IDA Elicits High Rates of Response in Newly Diagnosed AML

by SARA KARLOVITCH

THE ADDITION OF THE BCL2 inhibitor venetoclax (Venclexta) to fludarabine, cytarabine, idarubicin and G-CSF (FLAG-IDA) resulted in high complete response rates and enables a high consolidative allogeneic transplantation rate in patients with newly diagnosed acute myeloid leukemia (AML), according to data presented at the Society of Hematologic Oncology 2021 Annual Meeting.

Newly diagnosed patients with AML experience complete remission (CR) after FLAG-IDA induction at a rate of 85%, according to lead study author Curtis Lachowiez, MD, a hematology and medical oncology fellow at The University of Texas MD Anderson Cancer Center in Houston. With the addition of venetoclax investigators aimed to further improve response, reduce early mortality, and eradicate measurable residual disease.

Lachowiez presented results from the phase 2 portion of a phase 1b/2 study (NCT03214562) in which investigators evaluated the combination in patients with both newly diagnosed and relapsed/refractory AML. The analysis comes from the newly diagnosed cohort.

The overall response rate (ORR) for patients with newly diagnosed AML (n = 41) was 98%, with 73% of patients achieving CR. Composite CRs were seen in 88% of the population with 92% of these responders displaying minimal residual disease (MRD) negativity. The median OS was not reached (NR) at a median follow-up of 16 months (range, 12-19). The median event-free survival (EFS) was also NR (range, 18-NR) and the 12-month and 24-month EFS rates were 77% and 60%, respectively. The study has an estimated total enrollment of 116 patients. Primary end points include ORR up to 6 years, CR rate, hematologic response, duration of response, EFS, OS, antitumor activity, pharmacodynamic markers, drug exposure levels, and overall incidence and severity of all adverse events (AEs). The secondary end point is morphologic leukemia-free state.

The median age of the newly diagnosed AML cohort was 44 years (range, 20-65). Most of the patients were female (54%) and the median blast at enrollment was 46% (range, 4%-85%). In terms of histology, 71% of patients were those with de novo AML. Sixty-six percent of patients (n = 27) bridged to hematopoietic allogeneic stem cell transplantation (HSCT) at the time of analysis. At the median follow-up of 16 months (range, 15-23), median OS has yet to be reached in those who underwent HSCT. The median EFS has also not been reached by data cutoff. The 12-month EFS rate was 73% and the 24-month EFS rate was 60%. The median OS rate at 12 months was 95% and the 24-month OS rate was 82%. At a median follow-up of 7.4 months, for patients who did not undergo HSCT (n = 14), the 12-month EFS rate was 93%. The 24-month EFS rate was not available for this group. The 12- and 24-month OS rates were both 100%.

The emergence of a TP53 mutation was common at relapse than other mutations.

“Sixty-seven percent, or 6 out of 9 patients that have relapsed, had TP53 mutations. It is worth noting that 1 of the patients who have relapsed without a TP53 mutation also harbored an inversion 3 mutation,” Lachowiez said.

Infectious AEs were the most common associated with the regimen, specifically, febrile neutropenia (39%), pneumonia (24%), and bacteremia (19%). “We see that FLAG-IDA with venetoclax in newly diagnosed AML is associated with a high composite CR rate in de novo, secondary, and therapy-related AML,” Lachowiez said. “MRD negativity is attained in over 90% of patients who achieve the composite CR. FLAG-IDA with venetoclax is associated with an acceptable safety profile with infectious complications being most common and resulted in a high rate of transition to allogeneic transplantation to date.”

Table: Efficacy Results in the Newly Diagnosed AML Cohort of NCT03214562

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All patients (N=41)</th>
<th>de novo AML (n=29)</th>
<th>sAML/tAML (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>98%</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Composite CR</td>
<td>88%</td>
<td>83%</td>
<td>50%</td>
</tr>
<tr>
<td>MRD-negative composite CR</td>
<td>92%</td>
<td>92%</td>
<td>100%</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; CR, complete remission; MRD, minimal residual disease; ORR, overall response rate; sAML, systemic acute myeloid leukemia; tAML, therapy acute myeloid leukemia.

For patients who underwent HSCT, the median OS was NR, compared with 24.1 months (95% CI, 24-NR) in those who did not undergo transplant. The median EFS was NR for either group.

“Avoiding HSCT, the treatment is desirable,” Lachowiez said.

“The goal of combining venetoclax with FLAG-IDA is to improve OS and event-free survival (EFS),” Lachowiez said. “This combination significantly extends OS and event-free survival.”

The combination was effective across a variety of molecular subgroups, including NPM1, KMT2A, RUNX1, and IDH2; however, patients in these subgroups were at an increased risk of relapse. The emergence of a TP53 mutation was more common at relapse than other mutations.

Infectious AEs were the most common associated with the regimen, specifically, febrile neutropenia (39%), pneumonia (24%), and bacteremia (19%).

TP53 mutations were associated with worse EFS and OS. The combination was effective across a variety of molecular subgroups, including NPM1, KMT2A, RUNX1, and IDH2; however, patients in these subgroups were at an increased risk of relapse. The emergence of a TP53 mutation was more common at relapse than other mutations.

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REFERENCE
Pirtobrutinib Shows Impressive Efficacy in Previously Treated CLL/SLL

by GINA MAURO

PIRTOBRUNITIN (LOXO-305) SHOWS PROMISING efficacy signals across dose levels in previously treated patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), according to dose-escalation and dose-expansion findings from the phase 1/2 BRUIN study (NCT03740529) presented during the Society of Hematologic Oncology (SOHO) 2021 Annual Meeting.¹

Specifically, the overall response rate (ORR) was 62% (95% CI, 53%-71%) in patients with CLL/SLL who previously received a Bruton tyrosine kinase (BTK) inhibitor (n = 121); this included a 47% partial response (PR) rate and a 15% PR rate with lymphocytosis (PR-L). Thirty-four percent of patients had stable disease (SD). In the overall group of patients with CLL/SLL (n = 139), the ORR was 63% (95% CI, 55%-71%); the PR rate was 50%, the PR-L rate was 14%, and the SD rate was 32%.

Data also showed that the ORR with pirtobrutinib increased over time. For patients who had been on treatment for at least 10 months, the ORR increased to 86%.

“Pirtobrutinib demonstrates promising efficacy in patients with CLL and SLL who have previously [been] treated with all classes of available therapy, and responses were observed across all dose levels,” lead study author Catherine Callaghan Coombs, MD, assistant professor of medicine in the Division of Hematology at the University of North Carolina School of Medicine, said in a virtual presentation on the data. “Efficacy was independent of BTK C481 mutation status, the reason for prior BTK inhibitor discontinuation—whether progression or intolerance—or other classes of prior therapy received.”

Discontinuation of ibritinib (Imbruvica) remains a significant issue in the treatment paradigm of CLL, Coombs said, adding that 5-year discontinuation rates with the BTK inhibitor are 41% in the frontline setting² and 54% for those with relapsed/refractory disease.³ In most cases, progressive disease in CLL following covalent BTK inhibitors are BTK C481 mutations, which prevent covalent BTK inhibitors from achieving effective target inhibition.

Pirtobrutinib is a highly potent and selective noncovalent BTK inhibitor currently being evaluated in B-cell malignancies. It offers nanomolar potency against wild-type and C481-mutant BTK in cell and enzyme assays with greater than 300-fold selectivity for BTK vs 370 other kinases. Because of reversible binding mode, BTK inhibition is not affected by an intrinsic rate of BTK turnover, and its favorable pharmacologic properties allow for sustained BTK inhibition throughout the dosing interval.¹

In the ongoing phase 1/2 BRUIN trial, investigators are enrolling 323 patients with CLL, SLL, mantle cell lymphoma (MCL), Waldenström macroglobulinemia, and other B-cell non-Hodgkin lymphomas to receive pirtobrutinib at daily doses of 25 mg to 300 mg. The phase 1 portion of the trial included 203 patients and the phase 2 portion included 120 patients.

Data presented during the SOHO 2021 Annual Meeting focused on those in the CLL cohort; 170 patients were in the safety population and 139 were in the efficacy population. Assessment of 31 patients is ongoing prior to first restaging.

The phase 1 portion is a 3+3 design with 28-day cycles; intrapatient dose escalation is allowed, and cohort expansions are permitted at safe doses. The phase 2 portion of the trial is enrolling patients to receive the recommended phase 2 dose (RP2D) of pirtobrutinib, which was determined to be 200 mg daily.

To be eligible for enrollment patients had to be at least 18 years of age, have an ECOG performance status of 0 to 2, have CLL or another B-cell non-Hodgkin lymphoma, have active disease and be in need of therapy, and have received prior treatment.

The key end points of the trial are safety and tolerability, maximum-tolerated dose (MTD), RP2D, and pharmacokinetics, as well as ORR and duration of response based on International Workshop on CLL and International Workshop on Waldenström Macroglobulinemia, and Lugano Classification disease criteria.

The median age was 69 years (range, 36-88), and 36% of patients were female. Moreover, 51% of patients had an ECOG performance status of 0. The median number of prior therapies received was 3 (range, 1-11) overall, and was 4 (range, 1-11) in those who were previously treated with a BTK inhibitor.

Prior treatment consisted of a BTK inhibitor (86%), chemotherapy (82%), an anti-CD20 antibody (90%), a BCL2 inhibitor (34%), a PI3K inhibitor (21%), lenalidomide (Revlimid; 8%), allogeneic stem cell transplant (2%), and chimeric antigen receptor
Five responding patients had discontinued treatment and are in response. 94% of responding patients continued to receive treatment across the entire population, with a median follow-up of 6 months (range, 0.6-17.8). Additional findings showed that, at 5 years of follow-up from the phase 3 RESONATE-2 study, ORR of first-line ibrutinib treatment for patients with CLL/SLL: 5% (95% CI, 38%-66%).

Any-grade treatment-emergent AEs (TEAEs) included contusion (13%), diarrhea (17%), and fatigue (20%); 1 case of grade 3 fatigue was reported (TABLE 1). AEs of special interest included bruising (16%), rash (11%), arthralgia (5%), hemorrhage (5%), hypertension (5%), and atrial fibrillation/flutter (< 1%).

At the 2021 Pan Pacific Lymphoma Conference, data from the MCL cohort and other non-Hodgkin lymphomas of the phase 1/2 BRUIN study were presented (TABLE 2). Here, pirtobrutinib elicited an ORR of 52% (95% CI, 38%-65%) in patients with MCL (n = 56), with a 25% complete response (CR) rate, a 27% PR rate, and a SD rate of 18%.

In those who previously received a BTK inhibitor (n = 52), the ORR with pirtobrutinib was also 52% (95% CI, 38%-66%); the CR, PR, and SD rates were 25%, 27%, and 17%, respectively. In patients who previously underwent stem cell transplant or CAR T-cell therapy, the ORRs with the agent were 64% and 100%, respectively.

### TABLE 2. Response Rates in the Phase 1/2 BRUIN Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CLL/SLL cohort (n = 139)</th>
<th>CLL/SLL cohort with prior BTK inhibitor therapy (n = 121)</th>
<th>MCL cohort and other non-Hodgkin lymphomas (n = 56)</th>
<th>MCL cohort and other non-Hodgkin lymphomas with prior BTK inhibitor therapy (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>63% (55%-71%)</td>
<td>62% (52%-71%)</td>
<td>52% (38%-65%)</td>
<td>52% (38%-66%)</td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
<td>0%</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>PR</td>
<td>50%</td>
<td>47%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>PR-L</td>
<td>14%</td>
<td>15%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SD</td>
<td>32%</td>
<td>34%</td>
<td>18%</td>
<td>17%</td>
</tr>
</tbody>
</table>

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete remission; MCL, mantle cell lymphoma; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma.

Any-grade treatment-emergent AEs (TEAEs) included contusion (13%), diarrhea (17%), and fatigue (20%); 1 case of grade 3 fatigue was reported (TABLE 1). AEs of special interest included bruising (16%), rash (11%), arthralgia (5%), hemorrhage (5%), hypertension (5%), and atrial fibrillation/flutter (< 1%).

At the 2021 Pan Pacific Lymphoma Conference, data from the MCL cohort and other non-Hodgkin lymphomas of the phase 1/2 BRUIN study were presented (TABLE 2). Here, pirtobrutinib elicited an ORR of 52% (95% CI, 38%-65%) in patients with MCL (n = 56), with a 25% complete response (CR) rate, a 27% PR rate, and a SD rate of 18%.

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### REFERENCES

**INDICATION**
NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

**IMPORTANT SAFETY INFORMATION**
**Embryo-Fetal Toxicity:** Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

**Adverse Reactions**
Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%).

Clinically significant adverse reactions occurring in ≥ 2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs. 3.4% on placebo) and heart failure (2.1% vs. 0.9% on placebo).

**Drug Interactions**
Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA

**When treating non-metastatic castration-resistant prostate cancer (nmCRPC),**
Serious adverse reactions occurred in 25% of patients receiving NUBEQA for the treatment of non-metastatic castration-resistant prostate cancer. NUBEQA can cause fetal harm when administered to a pregnant woman. It is not known whether NUBEQA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NUBEQA is administered to a nursing woman.

INDICATION

NUBEQA is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer who have failed androgen deprivation therapy. NUBEQA is an inhibitor of the breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

NUBEQA®—Focus on both MFS and tolerability

More than double the median MFS with NUBEQA + ADT vs 18 months with ADT alone

(HR: 0.41; 95% CI: 0.34-0.50; P<0.0001) *95% CI: 34.3-NR. †95% CI: 15.5-22.3.

Three adverse reactions occurred more frequently with NUBEQA + ADT: fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%).

9% of men permanently discontinued due to adverse reactions whether on NUBEQA + ADT or ADT alone

Dose interruptions and reductions due to adverse reactions occurred in 13% and 6%, respectively, of patients treated with NUBEQA + ADT.

The most frequent reasons for permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%). The most frequent reasons for dose interruptions included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%). The most frequent reasons for dose reductions included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

NUBEQA®—proven to extend MFS, now with statistically significant OS

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone

Metastasis-free survival (MFS) was the primary endpoint. Overall survival (OS) was a key secondary endpoint. OS data were not mature at time of first analysis [57% of the required number of events]. At final analysis, OS was statistically significant but median not reached. HR: 0.69 (95% CI: 0.53-0.88; P=0.003).

Effects of NUBEQA on Other Drugs – NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

Please see the following pages for brief summary of full Prescribing Information.

Start new patients with up to 2 months free.

Visit NUBEQAhcp.com
NUBEQA® (darolutamide) tablets, for oral use

Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1)].

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS
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.

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA included urinary retention, pneumonia and hemorrhia. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

Table 1: Adverse Reactions in ARAMIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=554)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥ 3 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=554)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4%</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>AST</td>
<td>23</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)].

Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1)].

Infertility

Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m²). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hyposperma, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION
Dosage and Administration
Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity
Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

Infertility
Advise male patients that NUBEQA may impair fertility [see Use in Specific Populations (8.3)].

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For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

Investigators Aim to Fill Unmet Need of Intermediate- to High-Risk MDS With ENHANCE Trial

by KYLE DOHERTY

STANDARD-OF-CARE OPTIONS FOR patients with intermediate-, high-, and very high-risk myelodysplastic syndrome (MDS) have plateaued in their efficacy, leading investigators to seek alternative novel therapies. The initiation of the phase 3 ENHANCE trial (NCT04313881) looks to build on the generally early response to azacitidine with the addition of magrolimab, a first-in-class monoclonal antibody.1

“There are only 2 treatments available [for these patients],” said Eytan M. Stein, MD, a hematologic oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, in an interview with OncologyLive®. “These options are essentially 2 sides of the same coin. They are both hypomethylating agents; one is azacitidine [Vidaza] and the other is decitabine [Dacogen].”

Azacitidine was approved for all types of MDS in May 2004 based on results of the phase 3 Cancer and Leukemia Group B 9221 study in which the agent elicited a 16.2% response (n = 16/99) compared with no response with placebo (n = 0/92); response rates in similar single-arm studies ranged from 11.8% to 18.8%.2 Similar results were observed to support the FDA approval of decitabine in 2006; the response rate was 21% among 56 evaluable patients treated with the agent vs 0% in the supportive care arm (n = 89).3

“We know from clinical studies that were done about a decade ago that they’re better than doing nothing, which is what we had before these treatments,” Stein said. “But they’re certainly not good enough. The remission rate is in the range of 30% to 40%, [and] survival is somewhat limited. For this patient population, another key factor is that even in the patients who do respond to these drugs, they typically stop working after a year or two. The duration of response [DOR] is not particularly long. There’s a real need for new agents for MDS.”

ENHANCE will evaluate the efficacy of magrolimab in combination with azacitidine, compared with azacitidine plus placebo in previously untreated participants with intermediate-, high-, or very high-risk MDS.1 Preclinical models have shown synergistic effects of combining hypomethylating agents with immune checkpoint inhibitors, and investigators have hypothesized that the combination may overcome resistance mechanisms that arise with hypomethylating agents alone.4

Magrolimab blocks CD47, a key “do not eat me” signal that is often overexpressed on tumor cells. The binding of magrolimab to CD47 induces potent macrophage-mediated phagocytosis of tumor cells. Azacitidine synergizes with magrolimab by increasing expression of prophagocytic “eat me” signals.5–7

“There was a lot of good preclinical science that was done primarily in laboratory work by Ravi Majeti MD, PhD, at Stanford [University in California],” Stein noted. “This [preclinical work] showed that by giving an anti-CD47 antibody, you can get this immunologic approach where you can eradicate the MDS cells, the bad cells, that are causing the problem. The [inhibition of the] ‘do not eat me signal’ allows macrophages to basically recognize the malignant MDS cells, which then allows them to be eradicated through phagocytosis.”

FIGURE. Magrolimab Plus Azacitidine for Higher-Risk MDS
Phase 3 (NCT04313881)

Eligibility criteria
- Previously untreated individuals with intermediate- to very-high risk MDS by IPSS-R
- Adequate performance status and hematological, liver, and kidney function

Randomized 1:1
N = 520
Experimental
Magrolimab + azacitidine
Control
Placebo + azacitidine

End points
Primary
- CR
- OS
Select secondary
- Duration of CR
- ORR
- DOR
- RBC transfusion dependence
- PFS
- MRD-negativity response rate
- Time to transformation to AML
- AEs

AEs, adverse effects; AML, acute myeloid leukemia; CR, complete remission; DOR, duration of response; EFS, event-free survival; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RBC, red blood cell.
INITIAL SAFETY AND EFFICACY DATA OF MAGROLIMAB + AZACITIDINE

Investigators examined the combination of magrolimab and azacitidine in patients with hematological malignancies in a phase 1b trial (NCT03248479). A total of 39 patients with MDS have been treated with the combination. The median age of this cohort was 70 years (range, 47-80) and 13% of patients harbored a TP53 mutation.7

Magrolimab was given via a priming/intra-patient dose-escalation regimen of 1 to 30 mg/kg once a week for the first 2 cycles, then once every 2 weeks in cycles 3 and beyond. Azacitidine was administered at a dose of 75 mg/m² on days 1 to 7.

Among 33 patients evaluable for efficacy, the objective response rate (ORR) was 91% with 42% of responders achieving complete remission (CR). Several responses deepened over time; patients with at least a 6-month remission (CR). Several responses deepened the objective response rate (ORR) was 91% with 42% of responders achieving complete remission (CR). Several responses deepened over time; patients with at least a 6-month remission (CR).

Cytogenetic CRs were observed in 35% of efficacy-evaluable patients, with 91% of responding patients having a continuing response at 6 months. The median time to initial response was 1.9 months. Minimal residual disease negativity by multi-parameter flow cytometry was reported in 22% of patients with CR, CR with incomplete hematologic recovery, or marrow CR.7

Regarding safety, the most common adverse effects (AEs) of any grade were anemia (44%), fatigue (18%), infusion reaction (18%), and neutropenia (8%). No patients in the MDS cohort discontinued treatment because of an AE, and no treatment-related febrile neutropenia was seen by investigators.7

The median decrease in hemoglobin with the first dose of magrolimab plus azacitidine was 0.4 g/dL. Investigators noted that the combination had a similar safety profile compared with azacitidine monotherapy.7

“Magrolimab actually possesses a fairly good toxicity profile; it doesn’t have many significant AEs,” Stein said. “The most significant AE is that patients can experience an on-target anemia, which can be pretty dramatic at the onset. Also, in some patients, you can see the hemoglobin dropped by 2 to 3 grams.”

DETAILS OF THE ENHANCE TRIAL

The phase 3 trial will enroll approximately 520 previously untreated adult patients with intermediate-, high-, or very high-risk MDS by Revised International Prognostic Scoring System in the United States, Europe, Asia, and Australia [FIGURE]. To be eligible for the study, patients must have adequate performance status and hematological, liver, and kidney function. Patients will be evenly randomized to receive either magrolimab plus azacitidine or placebo plus azacitidine.1,8

Ineligible patients include those with active hepatitis B, C, and/or HIV after testing at screening or in their medical history. Patients previously treated with anti-CD47 or signal-regulatory protein α-targeting agents are not eligible for the trial. Patients with clinical suspicion of active central nervous system involvement or those who are pregnant or actively breastfeeding also will be excluded.8

Patients in the trial cannot have undergone any prior antileukemic therapy for treatment of intermediate-, high-, or very high-risk MDS. Patients with contraindications to azacitidine will be excluded, as well as those who have immediate eligibility for allogenic stem cell transplant with an available donor, as determined by the investigators.8

Patients in the experimental arm will receive a 1 mg/kg dose of magrolimab intravenously on days 1 and 4 of cycle 1, followed by 15 mg/kg on day 8, and 30 mg/kg on days 11, 15, and 22. In cycle 2, patients will be given 30 mg/kg of magrolimab on days 1, 8, 15, and 22. In cycle 3 and beyond, 30 mg/kg of magrolimab will be administered every 2 weeks on days 1 and 15.1,8

Stein said that a change in the trial design—treating patients frequently with smaller doses at the start—helped to curb some of the common AEs. “If this [dosing schedule], we believe that is going to help prevent this anemia that you may see,” he said.

In the control arm, placebo to match magrolimab will be administered intravenously. In both arms, azacitidine will be given at 75 mg/m² on days 1 to 7, or days 1 to 5 and 8 to 9 of each cycle, either subcutaneously or intravenously according to region-specific drug labeling.8

The primary end points of the trial are CR rate and overall survival. Key secondary end points include duration of CR, ORR, DOR, and progression-free survival. The trial is estimated to be completed by February 2025.8

“I believe magrolimab with azacitidine will become the standard of care,” Stein concluded. “If [the data] pan out in this phase 3 trial, it would be the first real immunotherapy/checkpoint inhibitor treatment for a myeloid malignancy. People talk about PD-L1 and PD-1 inhibitors in solid tumors [but] we haven’t had something that really works like that in patients with MDS or acute myeloid leukemia. If this [regimen] does work in the phase 3 setting, it’s a proof of concept that there is an immunologic therapy that you can give that can make outcomes in patients better in this class of diseases.” ■

REFERENCES

For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

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

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

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

ADC = antibody-drug conjugate; BCMA = B-cell maturation antigen; RRMM = relapsed or refractory multiple myeloma.

Learn more at BLENREPHCP.com
IMPORTANT SAFETY INFORMATION
WARRANTS 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 keratitits) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 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. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia 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.

Advertise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

ADVERSE REACTIONS

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

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP: keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

Renal or Hepatic Impairment: The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × 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.

**WARNIMG: 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 (6.2)].

**1 INDICATIONS AND USAGE**

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

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

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Ocular Toxicity**

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 169), 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), 38% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or loss 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 in 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.BLENREPREMS.com and 1-855-209-9188.

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

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

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

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

Dose reductions due to 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 lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

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

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

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

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial 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, asthenia, 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>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
</tr>
<tr>
<td>Creatine phosphokinase increased</td>
<td>22</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 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)
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 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 73% of patients aged 65 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)].

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:

• Patients must complete the enrollment form with their provider.

• Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Infusion-Related Reactions

• Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].

• Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].

• Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

Infertility

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

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August 2020 BPR:1BRS

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Adjuvant Pembrolizumab Continues to Uphold DFS Benefit Across RCC Subgroups

by GINA MAURO

PEMBROLIZUMAB (KEYTRUDA) AS adjuvant therapy compared with placebo continued to showcase an impressive disease-free survival (DFS) benefit in patients with clear cell renal cell carcinoma (RCC) following nephrectomy, with improvement observed across subgroups, according to data from the phase 3 KEYNOTE-564 trial (NCT03142334) were presented during the 2021 AUA Annual Meeting.¹

Findings showed that pembrolizumab improved DFS vs placebo across all prespecified subgroups, including region, type of nephrectomy, sarcomatoid features, disease risk category, tumor grade, and PD-L1 status. The benefit was most significantly pronounced in patients who underwent partial nephrectomy (HR, 0.22; 95% CI, 0.05-1.04) and those who had M1 no evidence of disease (NED; HR, 0.29; 95% CI, 0.12-0.69).

“Although numbers of participants with certain disease risk features were small, the DFS benefit was consistent across subgroups,” lead study author Toni K. Choueiri, MD, director of the Lank Center for Genitourinary Oncology, director of the Kidney Cancer Center, and senior physician at Dana-Farber Cancer Institute, as well as Jerome and Nancy Kohlberg chair and professor of medicine at Harvard Medical School in Boston, Massachusetts, said in a virtual presentation of the data. Choueiri is a 2021 Giants of Cancer Care® winner in the genitourinary cancer category.

Earlier findings from the KEYNOTE-564 study were presented during the 2021 American Society of Clinical Oncology Annual Meeting. Based on these data, the FDA granted a priority review designation to a new supplemental biologics license application for adjuvant pembrolizumab as a treatment for patients with RCC who are at intermediate-high or high risk of recurrence after nephrectomy or following nephrectomy and resection of metastatic lesions.² The agency is expected to decide on the application by December 10, 2021.

In the double-blind, multicenter, phase 3 KEYNOTE-564 study, investigators explored pembrolizumab vs placebo following nephrectomy in patients with clear cell RCC. Specifically, patients’ disease had to meet criteria that categorized them as intermediate-high risk for recurrence, which included: pT2, grade 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0; high-risk pT4, any grade, N0, M0; any PT, any grade, N-positive, M0; or M1 with NED after surgery.¹

Stratification factors included metastatic status (M0 vs M1 NED), as well as ECOG performance status (0 vs 1) and region (US vs non-US), both in the M0 group only.

To be eligible for enrollment, patients must have undergone nephrectomy within 12 weeks prior to randomization, could not have previously received systemic therapy, had to have an ECOG performance status of 0 or 1, and a tissue sample must have been obtainable for PD-L1 testing.

All patients underwent 1:1 randomization to receive pembrolizumab at 200 mg every 3 weeks or placebo every 3 weeks, both for approximately 1 year. The primary end point of the trial was investigator-assessed DFS; secondary end points were overall survival (OS) and safety.

The first prespecified interim analysis was planned after approximately 265 DFS events and a 12-month minimum follow-up. Following a minimum 15-month follow-up, 260 DFS events had occurred, and 51 OS events occurred. DFS and OS were estimated via Kaplan-Meier.

**TABLE 1. Efficacy Data for KEYNOTE-564**¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab (n = 496)</th>
<th>Placebo (n = 498)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DFS (95% CI)</td>
<td>NR (NR-NR)</td>
<td>NR (NR-NR)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.68; 95% CI, 0.53-0.87; P = 0.010</td>
<td></td>
</tr>
<tr>
<td>12-month DFS rate</td>
<td>85.7%</td>
<td>76.2%</td>
</tr>
<tr>
<td>24-month DFS rate</td>
<td>77.3%</td>
<td>68.1%</td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>NR (NR-NR)</td>
<td>NR (NR-NR)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.54; 95% CI, 0.30-0.96; P = 0.0164</td>
<td></td>
</tr>
<tr>
<td>12-month OS rate</td>
<td>98.6%</td>
<td>98.0%</td>
</tr>
<tr>
<td>24-month OS rate</td>
<td>96.6%</td>
<td>93.5%</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; NR, not reached; OS, overall survival.

**TABLE 2. Treatment-Related Adverse Effects in KEYNOTE-564**¹

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Pembrolizumab (n = 496)</th>
<th>Placebo (n = 498)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>20.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18.6%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>17.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15.8%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Rash</td>
<td>15.0%</td>
<td>7.3%</td>
</tr>
<tr>
<td>High-dose systemic corticosteroid treatment for immune-related adverse effects</td>
<td>7.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

<40 mg/day.
The median age of study participants was 60 years (range, 25-84), 71% of patients were male, and 73.5% had an ECOG performance status of 1. Moreover, 25.95% of patients were from North America, 37.7% were from the European Union, and 37.3% were from the rest of the world. Most patients (92.4%) underwent radical nephrectomy and 83.7% had absent sarcomatoid features.

Most patients (86.5%) had M0 intermediate-risk disease, 7.6% had M0 high-risk disease, and 5.8% had M1 NED. Moreover, 88.6% of patients had a primary tumor stage of T3; 3.5%, 30.4%, 43.5%, 22.3% of patients had tumor grade 1, 2, 3, and 4, respectively. Additionally, 93.8% of patients had N0 disease. Seventy-five percent of patients had a PD-L1 combined positive score of at least 1.

At a median follow-up of 24.1 months (range, 14.9-41.5), the median DFS in the intent-to-treat population was not reached with either pembrolizumab (n = 496) or placebo (n = 498) per investigator assessment (HR, 0.68; 95% CI, 0.53-0.87; *P* = .0010). The estimated 1-year DFS rates were 85.7% and 76.2% with pembrolizumab and placebo, respectively; the 2-year rates were 77.3% and 68.1%, respectively.

When examined across subgroups, additional factors that were associated with a more significant DFS benefit with pembrolizumab was patients of the European Union (HR, 0.49; 95% CI, 0.32-0.74), present sarcomatoid features (HR, 0.56; 95% CI, 0.29-1.06), and grade 4 tumors (HR, 0.57; 95% CI, 0.37-0.87).

OS data remain immature and the median OS has not yet been reached in either arm. However, there is a trend toward improved survival with pembrolizumab (HR, 0.49; 95% CI, 0.32-0.74), present sarcomatoid features (HR, 0.56; 95% CI, 0.29-1.06), and grade 4 tumors (HR, 0.57; 95% CI, 0.37-0.87).

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First- and second-generation EGFR TKIs have limited efficacy in patients with EGFR Exon20 insertion+ mNSCLC. Overall response rates when treated with first- and second-generation EGFR TKIs is <10%. Overall survival for EGFR Exon20 patients is half that of patients with common EGFR mutations when treated with first- and second-generation EGFR TKIs.

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De-escalation Strategies Help Personalize Care in HER2+ Breast Cancer

by RYAN SCOTT

THE INCORPORATION OF HER2-DIRECTED therapies into the treatment of patients with HER2-positive breast cancer has been revolutionary. Although benefits have been observed across histologic subtypes, investigative efforts in dosing regimens are needed. Specifically, treatments focused on de-escalating therapies for patients with lower-risk disease, and escalating options for those with higher-risk disease, according to Sara M. Tolaney, MD, MPH.

“HER2-positive disease was once thought to be the worst subtype of breast cancer, with the worst prognosis, but now [it might be] the subtype that has the best prognosis. This is because of our HER2-directed therapies,” said Tolaney, associate director, Susan F. Smith Center for Women’s Cancers; director, Clinical Trials, Breast Oncology; director, Breast Immunotherapy Clinical Research; and senior physician, at Dana-Farber Cancer Institute, in Boston, Massachusetts. “This shows what an impact these new agents are having, and it makes us hopeful that these therapies are likely to improve outcomes even further.”

In an interview with OncLive®, Tolaney, who is also an associate professor of medicine at Harvard Medical School, discusses progress made with escalation and de-escalation strategies in HER2-positive breast cancer, ongoing research with immunotherapy, and efforts being made to further move the needle forward.

**Q** What are some of the most recent advances that have optimized treatment strategies for patients with early HER2-positive breast cancer?

[Recent investigative efforts] have had a huge effect on patients with HER2-positive early-stage disease. However, as we have gotten better at introducing HER2-directed therapies into this setting, [we also have the] opportunity to figure out how best to personalize therapy for our patients. [This entails] trying to de-escalate the amount of toxic therapy given to patients with lower-risk disease, and trying to escalate therapy for those who have higher-risk disease. For example, those who have small HER2-positive, node-negative cancer are optimal [candidates] to consider giving less therapy to. Now that we have optimal HER2-directed agents, we are at a point where we can think about doing de-escalation. We have made tremendous headway in that area, but we can still do better.

<table>
<thead>
<tr>
<th>TABLE 1. Efficacy of Neratinib in ExteNET Trial†</th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>5-year iDFS absolute benefit</td>
</tr>
<tr>
<td>5-year DDFS absolute benefit</td>
</tr>
<tr>
<td>5-year CNS-DFS rate (95% CI)</td>
</tr>
<tr>
<td>5-year OS rate</td>
</tr>
<tr>
<td>8-year OS rate</td>
</tr>
</tbody>
</table>

**Q** **TABLE 1. Efficacy of Neratinib in ExteNET Trial†**

| **Outcome** | **Hormone receptor–positive ≤ 1 year with no pCR** |
|-----------------------------------------------|
| | **Neratinib** | **Placebo** |
| | (n = 131) | (n = 164) |
| 5-year cumulative incidence rate of CNS recurrence (95% CI) | 0.8% (0.1%-4.0%) | 3.6% (1.3%-7.8%) |
| 5-year iDFS rate (95% CI) | 85.0% (77.0%-90.4%) | 77.6% (69.8%-83.6%) |
| Absolute benefit | +7.4% | HR, 0.60 (95% CI, 0.33-1.07) |
| 5-year DDFS rate (95% CI) | 86.8% (79.0%-91.9%) | 79.8% (72.1%-85.6%) |
| Absolute benefit | +7.0% | HR, 0.61 (95% CI, 0.33-1.11) |
| 5-year CNS-DFS rate (95% CI) | 98.4% (93.6%-99.6%) | 92.0% (85.6%-95.7%) |
| 5-year OS rate | 95.1% | 85.6% |
| 8-year OS rate | 91.3% | 82.2% |

CNS, central nervous system; DDFS, distant disease-free survival; DFS, disease-free survival; OS, overall survival; pCR, pathologic complete response.

†Post trastuzumab.

In terms of escalation, we have also found that we can add HER2-directed therapies, such as we have with pertuzumab [Perjeta]. We [have also found] that it is possible to substitute more potent and effective HER2-directed therapies like ado-trastuzumab emtansine [T-DM1; Kadcyla] for trastuzumab [Herceptin]. Again, we have learned a lot about how to escalate therapy to improve outcomes, however, multiple ongoing trials are trying to do this even better with newer HER2-directed agents, such as trastuzumab deruxtecan [Enhertu] or tucatinib [Tukysa]. We are going to continue to
see more and more improvement in this area, which is exciting.

Q Please expand on some of the data that have been reported thus far with de-escalation treatment strategies. Has anything been learned regarding optimal duration of treatment?

[One strategy] has been to give less chemotherapy, which is important. [We have been able to do this in] stage I HER2-positive disease; options now include only giving paclitaxel and trastuzumab or giving just T-DM1 in this population. We have also tried to substitute more toxic chemotherapy with less toxic chemotherapy. For example, getting rid of anthracyclines would be a major improvement, and we have gotten a lot better at that. Most of us have now started using docetaxel, carboplatin, trastuzumab, and pertuzumab instead of doxorubicin and cyclophosphamide followed by paclitaxel, trastuzumab, and pertuzumab because data suggest that outcomes are similar with non-anthracycline-compared with anthracycline-based therapies.

An area that needs improvement [in terms of] de-escalation, and where there has not been much headway made, is duration of therapy. Currently, the standard of care is 1 year of trastuzumab-based treatment, which is a very long time. Although we have tried to do noninferiority studies with a shorter duration of trastuzumab, for most of these studies, it has not proven to be noninferior.

However, as we get better with HER2-directed therapies, it calls to question whether the full duration of therapy is needed with some of these treatments. For example, if someone achieves a pathologic complete response [pCR] to preoperative therapy, would we need to give them a full year of HER2-directed treatment? These are areas we can learn to do better in.

What is known about escalation approaches, specifically with neratinib (Nerlynx)?

One escalation strategy has been to take a patient who has high-risk HER2-positive disease who has completed all their HER2-directed therapy, as was done in the phase 3 ExteNET trial [NCT00878709], could we give them more therapy? ExteNET looked at giving 1 full year of neratinib vs placebo to patients who completed 1 year of trastuzumab. [Results showed] that in the [patients with] hormone receptor [HR]-positive, HER2-positive [disease], the year of neratinib significantly improved invasive disease-free survival [iDFS].

Since then, several interesting exploratory analyses have shown that if [we look at] really high-risk group, such as those with HR-positive, HER2-positive disease who did not achieve a pCR and were within the 6 months of completion of trastuzumab [when starting neratinib, there is] significant iDFS benefit, as well as an overall survival benefit. This is an intriguing finding. Moreover, they also saw numerically fewer brain metastases as first site of recurrence, [making this] the first study to show an impact on incidence of central nervous system metastases based on adjuvant therapy [TABLE 1].

This shows that we can do better. As such, more trials, like the ongoing phase 3 CompassHER2 RD study [NCT04457596], is adding tucatinib to T-DM1 in the residual disease population. We hope that the tucatinib will help prevent brain metastases on top of preventing recurrence.

Although some signals of benefit for immunotherapy [have been observed] in the metastatic setting, particularly with some data suggesting benefit with adding checkpoint inhibition to T-DM1, data in the early-stage setting from the phase 3 IMpassion050 trial [NCT03726879] which did not show benefit with adding atezolizumab [Tecentriq] to chemotherapy with trastuzumab and pertuzumab. This is a preoperative study that had a pCR end point, and most think event-free survival is the right end point now for these studies, so it is hard to know with certainty, but it was disappointing [TABLE 2].

Several other immunotherapy-based trials are ongoing, and they are looking at adding checkpoint inhibitors to both the preoperative and adjuvant settings. As such, we will learn more [from these studies], but for now, the signal [of benefit from immunotherapy] has not quite been there.

Q What other efforts have generated excitement in this paradigm?

We are also seeing studies looking at using more potent antibody-drug conjugates [ADCs] in the early disease setting, such as trastuzumab deruxtecan. An ongoing trial is looking to replace T-DM1 in the [adjuvant] setting with trastuzumab deruxtecan, which will teach us if we can do better by using a better ADC here.

Additionally, some trials [are examining] add-on strategies like CompassHER2 studies.

### TABLE 1. Updated Results of IMpassion050

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atezolizumab* (n = 228)</th>
<th>Placebo* (n = 226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year EFS rate (95% CI)</td>
<td>97.9% (95.8%-99.9%)</td>
<td>96.3% (93.8%-96.8%)</td>
</tr>
</tbody>
</table>

EFS, event-free survival; pCR, pathologic complete response.

* Therapy is in addition to pertuzumab, trastuzumab, and chemotherapy.

### TABLE 2. Updated Results of IMpassion050

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atezolizumab* (n = 109)</th>
<th>Placebo* (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year EFS rate (95% CI)</td>
<td>97.9% (95.8%-99.9%)</td>
<td>96.3% (93.8%-96.8%)</td>
</tr>
</tbody>
</table>

EFS, event-free survival; pCR, pathologic complete response.

* Therapy is in addition to pertuzumab, trastuzumab, and chemotherapy.
Darolutamide Delays Time to Deterioration in Urinary and Bowel Symptoms in nmCRPC

by BENJAMIN SAYLOR

Darolutamide (Nubeqa) was linked with a reduction in locally invasive procedures, delayed time to deterioration in health-related quality of life (HRQOL) related to urinary and bowel symptoms in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC), according to data from an analysis presented during the 2021 American Urological Association Annual Meeting.

For the study, investigators evaluated the effect of darolutamide on local symptom control. Specifically, they examined incidence and time to first prostate cancer-related invasive procedures, time to deterioration in HRQOL measures, and incidence of urinary and bowel treatment-related adverse effects and their correlation with prostate-specific antigen (PSA) decline from baseline to week 16 in patients receiving darolutamide.

Time to deterioration in HRQOL measures was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Prostate Cancer Module and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) prostate cancer subscale.

“The results of these analyses showed that fewer patients receiving darolutamide, 4.7%, underwent locally invasive procedures compared with patients receiving placebo, 9.6%,” said first author Neal D. Shore, MD, FACS, director of Carolina Urologic Research Center in Myrtle Beach, South Carolina. The most common procedures included catheterization, transurethral resection of the prostate, nephrostomy, and surgical excisions and resections.

Darolutamide significantly prolonged the time to first prostate cancer-related locally invasive procedure compared with placebo (HR, 0.42; 95% CI, 0.28-0.62) and delayed the time to deterioration of total bowel symptoms vs placebo (HR, 0.781; 95% CI, 0.664-0.918).

“For the EORTC urinary symptom subscale, darolutamide significantly delayed the time to deterioration in quality of life for total urinary symptoms and for each individual question about urinary symptoms versus placebo,” Shore said.

The 4 questions that contributed the most to the delay in time to deterioration of HRQOL with darolutamide included as follows:

- Do you urinate frequently during the day? (HR, 0.764; 95% CI, 0.648-0.902);
- Do you urinate frequently at night? (HR, 0.664; 95% CI, 0.559-0.790);
- Do you experience pain when urinating? (HR, 0.569; 95% CI, 0.441-0.734);
- Do urinary problems interfere with daily activities? (HR, 0.748; 95% CI, 0.614-0.910)

Regarding the FACT-P Prostate Cancer Subscale, darolutamide significantly delayed time to deterioration for total urinary symptoms as well as for each of the 3 urinary symptom questions. The time to deterioration in trouble moving bowels was not significantly affected by treatment with darolutamide (HR, 1.089; 95% CI, 0.862-1.376).

In the overall study population, urinary retention occurred in 36 patients (3.8%) in the treatment arm vs 41 patients (7.4%) in the placebo arm. Dysuria occurred in 25 patients (2.6%) in the treatment arm vs 29 patients (5.2%) in the placebo arm.

“The incidences of other urinary and bowel adverse effects showed minimal differences of 2% or less between treatments,” Shore said.

In addition, for patients treated with darolutamide, greater prostate-specific antigen response was associated with a lower incidence of urinary retention and dysuria. Specifically, patients receiving darolutamide who had a PSA decline of 90% or greater from baseline to week 16 had incidences of urinary retention and dysuria of 2.2% and 0.5% respectively compared with 5.1% for urinary retention and dysuria in patients with a PSA response of less than 50%.

“In conclusion, darolutamide was associated with a reduction in locally invasive procedures and delayed time to deterioration in patient health-related quality of life with respect to urinary and bowel symptoms. No increase in urinary and bowel-related adverse events compared with placebo confirms the favorable safety profile of darolutamide. These findings demonstrate that darolutamide had a positive effect on local disease recurrence and symptom control in patients with nonmetastatic CRPC,” Shore said.
Nearly 5 years

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Digital Health and Process Improvements Enhance Community-Based Patient Care

by LALAN S. WILFONG, MD; and AMILA PATEL, PharmD, BCOP

A MARKED REDUCTION in hospitalizations and emergency department (ED) visits are key metrics for value-based care programs. Quality improvement processes and electronic patient management systems may give practices a way to fully embrace these programs and remain mindful of cost while ensuring that patients receive high-quality care.

Investigators at Texas Oncology, a member of The US Oncology Network, piloted a quality initiative to evaluate health care resource use.¹ A review of the data revealed that the majority of hospitalizations and ED visits occurred during normal business hours. Texas Oncology investigators considered various options aimed at improving outcomes, such as extended hours, but decided to first determine why patients were opting for visits to the ED when a visit to the clinic may have met their needs.

A second issue worthy of investigation was patient complaints regarding the timeliness of returning phone calls. Changes implemented at the practice prioritized improving the management of patient calls, and required comprehensive insight into call volumes, nurse burden, and callback times. Without a practice-wide system to monitor and track calls across different locations the statewide cancer care provider, which has more than 200 locations and more than 500 physicians, sought to implement uniform systems and procedures.

Once they had determined that delayed callback times often led to ED visits for symptoms that could be managed in the clinical setting, the Texas Oncology investigators began searching for a solution to improve call timeliness. Their search culminated in a highly successful collaboration with Navigating Cancer, a health care technology company with an electronic patient management system to efficiently track, monitor, and triage patient calls.

EXECUTING THE SOLUTION
Navigating Cancer’s oncology-specific digital health technology includes a care management platform that
integrates clinic workflows, enabling staff to easily document, track, and escalate all inbound patient outreach. Overall, the system enables more seamless communication between patients and care providers when patients are away from the clinic. Its implementation was conducted in a stepwise manner across Texas Oncology's 200-plus locations, beginning in Q3 of 2019 and being completed in Q1 2020. To evaluate improvement in incident resolution times, an implementation study was launched, tracking resolution times for all incidents through December 2020.

For each practice's locations, call volume was estimated based on clinic volume; triage nurses and operators were reallocated or hired accordingly. Incoming calls were entered into the Navigating Cancer dashboard as incidents. Operators then followed system-generated prompts and routed calls to the appropriate staff based on symptom priority. Incident volume and resolution times were tracked by the system.

Practice leadership recommended callback time thresholds, aiming for a less than 90-minute resolution for symptom-related incidents. A root cause analysis of delays in callback times was conducted at each location. Plan-Do-Study-Act (PDSA) cycles were instituted and quality improvement processes implemented. For example, improving communication between triage nurses and physicians during clinic hours was a common theme that required changes in communication styles at various locations. Ongoing monitoring and tracking of resolution times enabled a continuous cycle of quality improvement.

The electronic care management platform also allowed the practice to continue the initiative during the COVID-19 pandemic, as staff were able to work remotely. If a potential ED visit was avoided, nurses documented the information and these data points allowed the practice to establish comprehensive strategic action plans for quality improvement.

**SOLUTION DRIVES DRAMATIC IMPROVEMENTS**

Navigating Cancer’s technology solution addressed more than 1 million incidents for more than 400,000 patients in just 1 year (TABLE). The results of the implementation were impressive, especially as the pandemic was disrupting health care at the same time. A few of the most noteworthy findings include the following:

- Significant growth occurred in the volume of inbound calls to the practice from the first half of the year to the second, likely a consequence of the shift to more remote care during the pandemic.
- Callback times improved by more than 2 hours from the start of the implementation process to the end. This demonstrates the success of PDSA cycles and the collaboration between the practice and Navigating Cancer to continuously drive process and technology improvements.
- More than 60% of symptom-related issues were addressed in less than 1 hour—a significant improvement for Texas Oncology.
- Eight percent of symptom-related incidents resulted in definite or probable ED avoidance following assessment by a nurse. Shortness of breath, vomiting, chills, and weakness were the top symptoms addressed for ED avoidance.

**USING DATA TO BUILD QUALITY INITIATIVES**

The Navigating Cancer system created robust data to drive quality improvements and provide a foundation for future initiatives. For instance, data played a key role in PDSA cycle improvements, with data from each location being made available to practice directors at all locations. This created friendly competition and drove improvement, as no one wanted to be last on the list.

The investigators are examining data to identify other possible improvements. They are scrutinizing the types of calls to determine whether anything should be done differently based on patient symptoms and outcomes. This includes, for example, how the system could be optimized to appropriately triage and resolve 1 patient’s report of pain vs another patient’s report of nausea and vomiting.

The investigators are also evaluating data for call routing to develop strategies to improve processes. Patients often ask for a nurse regardless of the issue, as they know the nurse will return their call. By making sure operators have the right tools to route calls appropriately, nurses will only address nursing-specific calls. Other calls will be routed to the appropriate staff for scheduling issues or financial concerns, among other issues, increasing efficiency in all areas.

Members of Texas Oncology and Navigating Cancer will evaluate the effect of their system against health care resource utilization, measuring both ED visits and outcome implementation period.

**TABLE. Triage Incident Resolutions**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Implementation period</th>
<th>Postimplementation period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q3 2019</td>
<td>Q1-Q4 2020</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>16,848</td>
<td>412,750</td>
</tr>
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</tr>
<tr>
<td>Mean resolution time, hours</td>
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<td>2.22</td>
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<tr>
<td>Symptom incidents</td>
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<td>1.49</td>
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<tr>
<td>Categorical symptom incident resolution time, n (%)</td>
<td></td>
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<tr>
<td>&lt; 1 hour</td>
<td>2717 (55.2%)</td>
<td>66,151 (61.6%)</td>
</tr>
<tr>
<td>&gt; 1 hour</td>
<td>2205 (44.8%)</td>
<td>41,251 (38.4%)</td>
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<tr>
<td>Symptom incident emergency department avoidances, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely</td>
<td>321 (0%)</td>
<td>1508 (1.4%)</td>
</tr>
<tr>
<td>Probably</td>
<td>844 (2.7%)</td>
<td>6979 (6.5%)</td>
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<tr>
<td>No</td>
<td>21,704 (68.8%)</td>
<td>66,769 (62.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8689 (27.5%)</td>
<td>32,300 (30.0%)</td>
</tr>
</tbody>
</table>
hospitalizations. As data are often delayed, information will most likely not be available for analysis until next year.

**FOCUSBING ON IMPROVEMENT ACTIVITIES CAN DRIVE BETTER CARE**

Tackling a problem such as ED visits during business hours requires a deep dive into why patients go in the first place and what can be done to address adverse effects before they become unmanageable.

During this program callbacks were not happening promptly enough, resulting in patients visiting the ED rather than the clinic. Despite tremendous growth in calls and issues during the tracking period, implementing the Navigating Cancer solution and ongoing quality improvement strategies allowed the practice to shorten callback times. Such focused attention on improvements demonstrated that positive changes, even during a global pandemic, are possible. Based on nurse assessment, this improvement is showing trends toward reduced ED visits and hopefully will be verified based on claims data sets.

The successful implementation of the Navigating Cancer solution is a great example of how technology empowers practices to provide better care, improve outcomes, and reduce resource utilization. Texas Oncology’s use of this digital technology to shorten callback times enables patients to be treated in the clinic by a care team they know and trust, rather than experiencing a costly and somewhat distressing ED or hospital visit.

**Lalan S. Wilfong, MD, is vice president of payer relations and practice transformation at McKesson Specialty Health. **Amila Patel, PharmD, BCOP, is senior director of clinical innovation at Navigating Cancer.

**REFERENCE**


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**The Waiting Room Revolution**

by KEITH A. REYNOLDS

**THE COVID-19 PANDEMIC LED to a near-overnight revolution in many parts of health care, and nowhere was this seen more than in the waiting room. Now that things have changed, what does the future hold?**

“It always needed to change a little bit because it’s hard to manage a waiting room,” said David Berg, president and cofounder of Redirect Health, in an interview with *Medical Economics*. “When [the COVID-19 pandemic] hit, it had to change. We had no choice. If it was once just an annoying or irritating place to be, the waiting room became a dangerous place to be.”

**How has COVID-19 changed the way patients wait for their appointments?**

The biggest way we had to change is we had to figure out [which] parts we could do virtually or remotely. We had to figure out how we could do those and separate them from the office visit. For instance, when you walk up to the front desk and you want to ask what your co-pay is or you want to pay your co-pay, there’s no reason that can’t be done over the phone from your home. When the nurse or the medical assistant is confirming your medication list to make sure that they have it right in the chart…that doesn’t have to happen in the office—it can happen over the phone.

There are many parts of the in-office visit that, if we segment it appropriately, can be done beforehand at home. Whether it’s chart prep, taking history, or verifying medications…so many things we used to do in the exam or waiting room now can happen on your drive in to see us, at work, or the day before at home.

We’ve all heard of drive-through COVID-19 testing, which didn’t happen before [the pandemic]. I [received] my vaccination sitting in my car...it became highly necessary when the exam rooms and waiting rooms became dangerous because of the risk of infection and the uncertainty of it.

**What can physicians do to make the waiting room experience better?**

The obvious [thing] is to eliminate the amount of time in it. An easy way of doing that is to have [patients] sit in their car until you’re ready for them, and then ping them and let them walk up a couple minutes before and take them right in. Why is that advantageous? Well, some [patients] like to work while they’re waiting, and it could be easier to be on a phone call in the car than in a waiting room. Some offices don’t even like [patients] talking on cell phones in their waiting rooms, but in the car, you have a lot more freedom to do the things that you want to do. Similarly, at home, you have a lot more freedom.

Now [patients] have become used to not waiting for doctors...They’ve got a little taste of that convenience and that freedom; I don’t think they will go back.

This transcript has been edited for clarity and length. To read the full interview, visit bit.ly/3hvKsCj.
Building MOMENTUM for Patients with Myelofibrosis

If you are interested in learning more about the MOMENTUM Clinical Trial for Patients with Myelofibrosis and determining if your patients may be eligible, please contact a MOMENTUM Trial representative by visiting momentumtrial.com/for-physicians
Pivotal Trial Results Look to Shake up HCC Treatment Landscape

by AMIT MAHIPAL, MBBS; and RICHARD KIM, MD

HEPATOCELLULAR CANCER (HCC), the most common primary liver malignancy, is the fourth-leading cause of cancer-related deaths globally. HCC is a heterogeneous malignancy resulting from diverse causes of chronic liver injury and cirrhosis, with viral hepatitis, alcoholic cirrhosis, nonalcoholic steatohepatitis, and hemochromatosis being the most common etiologic factors. Despite recent advancements in the treatment of HCC, the 5-year survival rate is less than 20%. Surgery and liver transplantation are the primary curative modalities for patients with early-stage HCC; however, a majority of patients with HCC are not amenable for surgical resection or locoregional therapy including ablation, embolization, or radiation therapy.

Until recently, systemic therapeutic options were limited for patients with advanced HCC—sorafenib (Nexavar) was the only FDA-approved therapy for more than a decade. Immunotherapy, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies targeting VEGF have all received FDA approval, broadening the plethora of treatment options for this patient population.

For patients with advanced HCC not amenable for surgical resection, treatment options include locoregional or systemic therapy; there is no role for adjuvant therapy following surgical resection or locoregional therapy for HCC. Investigators are evaluating the role of immune checkpoint inhibitors as adjuvant therapy post surgery, ablation, and embolization in multiple trials. In addition to the stage of disease, performance status and comorbidities, treatment of HCC is guided by Child-Pugh score and Barcelona Clinic Liver Cancer (BCLC) staging system. Historically, locoregional treatment is recommended for patients with BCLC stage B and systemic therapy for BCLC stage C. Benefit of systemic therapy is primarily limited to patients with Child-Pugh score A5 or A6.

FIRST-LINE TREATMENT

Sorafenib was approved by the FDA based on data from the phase 3 SHARP trial (NCT00105443), which demonstrated an improved median overall survival (OS) of 10.7 months vs 7.9 months with placebo (HR, 0.69; 95% CI, 0.55-0.87; P < .001); the median time to radiologic progression was 5.5 months vs 2.8 months, respectively (HR, 0.58; 95% CI, 0.45-0.74; P < .001). These results were validated in another randomized trial (NCT00492752) conducted in the Asia-Pacific region. For nearly a decade after the SHARP trial, no targeted therapy demonstrated survival benefit compared with sorafenib as first-line therapy.

Lenvatinib (Lenvima), a small molecular tyrosine kinase inhibitor targeting VEGF, FGFR, PDGFR, RET and c-kit, was compared with sorafenib in a phase 3 randomized inferiority trial (NCT01761266) that included 1492 eligible patients. Lenvatinib was associated with improved median progression-free survival (PFS) of 7.4 months (95% CI, 6.9-8.8) vs 3.7 months (95% CI, 3.6-4.6) with sorafenib. The objective response rate (ORR) for patients treated with lenvatinib (n = 478) was 24.1% vs 9.2% with sorafenib (n = 476); however, a similar median OS was reported at 13.6 (95% CI, 12.1-14.9) vs 12.3 months (95% CI, 10.4-13.9), respectively (HR, 0.92; 95% CI, 0.79-1.06). Treatment-related adverse events were similar in both arms. This trial led to FDA approval of lenvatinib for patients with advanced HCC in first-line setting.

Promising activity of immune checkpoint inhibitors in a phase 2 trial led to multiple phase 3 trials in first and later lines of treatment (TABLE 1-3,5-9). Investigators of IMbrave150 (NCT03434379), a phase 3 trial, randomized patients with advanced HCC in 2:1 fashion to atezolizumab (Tecentriq) plus bevacizumab (Avastin) and sorafenib arms, respectively. The combination of atezolizumab plus bevacizumab was associated with improved OS (HR, 0.58; 95% CI, 0.42-0.79; P < .001) with 12-month OS rate of 67.2% with the combination (n = 336) compared with 54.6% with sorafenib (n = 165). The median PFS was 6.8 months (95% CI, 5.7-8.3) in the combination arm compared with 4.3 months (95% CI, 4.0-5.6) in the control arm. Notably, patients were excluded if they had untreated or incompletely treated esophageal or gastric varices, autoimmune disease, or coinfection with hepatitis B or C.

In contrast to above trial, the phase 3 CheckMate 459 trial (NCT02576509) failed to demonstrate a significant survival benefit for nivolumab compared with sorafenib as first-line therapy in unselected patients with HCC. Subgroup analysis did suggest potential benefit in patients who had PD-L1-positive tumors.

Combination therapy with lenvatinib plus pembrolizumab (Keytruda) has demonstrated promising activity. Among 100 treated patients the doublet elicited an ORR of 46% (95% CI, 36.0%-56.3%), a median PFS of 9.3 months (95% CI, 5.6-9.7), and a median OS of 22 months (95% CI, 20.4-not estimable) in a single-arm trial (NCT03006926). Based on these exciting results, a
A phase 3 trial evaluating this combination is under way (LEAP-002; NCT03713593).

**SECOND-LINE TREATMENT**

Multiple therapeutic agents are approved for patients with advanced HCC progressing or intolerant to first-line therapy with sorafenib. Regorafenib (Stivarga), cabozantinib (Cabometyx), and ramucirumab (Cyramza), all targeting VEGFR, were approved based on results of randomized phase 3 trials that demonstrated a survival benefit when compared with placebo. The median OS in the experimental arms in these trials was in the range of 8.5 to 10.6 months.

There were some differences in eligibility criteria in these trials. For example, in the RESORCE study (NCT01774344), which compared regorafenib with placebo, patients were excluded if they discontinued sorafenib because of adverse events. To be eligible for the REACH-2 trial (NCT02435433) evaluating ramucirumab, patients should have α-fetoprotein (AFP) levels greater than 400 ng/mL (or > 1.5 times the upper limit). In contrast, the CELESTIAL trial (NCT01908426), which randomized patients to cabozantinib or placebo, is the only randomized trial that allowed patients who had received prior immunotherapy to be eligible.

| TABLE. Select Phase 3 Trials for Patients With Advanced Hepatocellular Cancer | | |
|---|---|---|---|---|---|---|---|---|
| Trial (ClinicalTrials.gov identifier) | Line of therapy | Therapeutic agents | N | PFS (months) | OS (months) |
| SHARP (NCT00105443) | First | Sorafenib vs placebo | 602 | TTP: 5.5 vs 2.8 | 10.7 vs 7.9 |
| NCT00492752 | First | Sorafenib vs placebo | 226 | TTP: 2.8 vs 1.4 | 6.5 vs 4.2 |
| NCT01761266 | First | Lenvatinib vs sorafenib | 954 | 7.4 vs 3.7 | 13.6 vs 12.3* |
| IMbrave150 (NCT03434379) | First | Atezolizumab plus bevacizumab vs sorafenib | 588 | 6.8 vs 4.3 | NR vs 13.2 |
| CheckMate 459 (NCT02576509) | First | Nivolumab vs sorafenib | 743 | 3.7 vs 3.8* | 16.7 vs 15.2* |
| RESORCE (NCT01774344) | Second | Regorafenib vs placebo | 573 | 3.1 vs 1.5 | 10.6 vs 7.8 |
| CELESTIAL (NCT01908426) | Second or later | Cabozantinib vs placebo | 707 | 5.2 vs 1.9 | 10.2 vs 8.0 |
| REACH-2 (NCT02435433) | Second | Ramucirumab vs placebo | 403 | 2.8 vs 1.6 | 8.5 vs 7.3 |
| KEYNOTE-240 (NCT02702401) | Second | Pembrolizumab vs placebo | 413 | 3.0 vs 2.8* | 13.9 vs 10.6* |

NR, not reached; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

*Did not reach statistical significance.

**SEQUENCING OF THERAPY**

Systemic therapeutic strategy for advanced HCC continues to evolve. For patients with no contraindication to immunotherapy and without untreated gastroesophageal varices, combination of atezolizumab plus bevacizumab is the recommended first-line treatment. For patients who are ineligible to receive this combination, either lenvatinib or sorafenib is a reasonable choice. There is a lack of published data to suggest a preferred treatment option after progression on a single-agent regimen.
atezolizumab plus bevacizumab. Thus, optimal treatment sequencing strategy remains undefined.

Our recommendation is to consider atezolizumab plus bevacizumab as first-line therapy; followed by TKI including lenvatinib, sorafenib, cabozantinib or regorafenib as second-line therapy; followed by another TKI which was not used in second regorafenib, cabozantinib, or ramucirumab as third line (FIGURE). Patients enrolled in the CELESTIAL trial, which examined the efficacy of cabozantinib, could receive more than 1 line of prior therapy, including immunotherapy. If sorafenib was well-tolerated and patients had prolonged disease control, they may preferentially benefit from regorafenib as next line of therapy. The combination of ipilimumab plus nivolumab has demonstrated promising activity but remains untested in patients treated with prior checkpoint inhibitors. Similarly, efficacy of ramucirumab remains unclear in patients who failed bevacizumab in the first line.

FUTURE DIRECTIONS
There are several areas of unmet need for patients with advanced HCC. For example, benefit with systemic therapy is limited to patients with good performance status with Child-Pugh score 7 or lower, excluding a vast proportion of patients. The development of promising systemic therapies with manageable adverse event profiles suggests that investigators should compare these systemic options with locoregional therapy for patients with high-risk disease. Finally, there is an urgent need to develop biomarkers that can help in selecting patients for different treatment options.

Global Liver Institute (GLI) is the only liver-focused nonprofit organization operating in both the United States and Europe. GLI’s mission is to improve the lives of individuals and families affected by liver disease through promoting innovation, encouraging collaboration, and scaling optimal approaches to help eradicate liver diseases. By working across disease states and convening all stakeholders, GLI aims to amplify the voices of those affected by liver diseases and cancers. One of these initiatives is GLI’s Liver Cancers Council. Richard Kim, MD, is an active and engaged member helping to lead the charge for patient advocacy. For more information and resources please visit https://globalliver.org.

REFERENCES
Initial Guideline Development Showcases Directions in Ultrarare Sarcoma Subtype

by JESSICA HERGERT

AS PART OF A GLOBAL consensus meeting, experts from several disciplines convened to define evidence-based guidelines for the treatment of patients with primary and metastatic epithelioid hemangioendothelioma (EHE) with locoregional and systemic therapies. These recommendations also provide guidance on palliative care, according to the resultant consensus paper published in *ESMO Open Cancer Horizons.*

“The degree of uncertainty in selecting the most appropriate therapy for patients [with EHE] and the lack of guidelines on the clinical management of the disease make the adoption of new treatments inconsistent across the world, resulting in suboptimal outcomes for many,” lead study author Silvia Stacchiotti, MD, a medical oncologist in the Adult Mesenchymal Tumor and Rare Cancer Unit of the Cancer Medicine Department at the Fondazione IRCCS Istituto Nazionale Tumori in Milan, Italy, and coauthors wrote.

EHE is an ultrarare subtype of translocated, vascular sarcoma that can present as a low- or high-grade malignancy anywhere in the body. The disease is characterized by an epithelioid endothelial cell population located in a distinctive myxohyaline stroma that harbors *WWTR1-CAMTA1* or *YAP1-TFE3* gene fusions. Currently, no systemic therapies are approved for specific use in EHE, but patients with EHE are often refractory to traditional sarcoma therapies.

“EHE is a very complicated disease,” study author William D. Tap, MD, a medical oncologist and chief of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering Cancer Center in New York, New York, said in a news release. “Some [individuals] can have very slow-growing disease and can go for long periods without treatment. Or they may do very well with surgery to remove the tumor and nothing else. But for others, it can be very aggressive and dangerous.”

Because of EHE’s rarity and lack of available therapies, establishing clinical guidelines for management of the disease has been challenging, and therapeutic approaches to treating patients with EHE vary globally.

Notably, no randomized phase 2 or 3 studies have ever been conducted in EHE. Data from 2 phase 2 studies are available, but the quality of evidence is lacking compared with that in common cancer types. Moreover, most clinical decisions in EHE are based on retrospective findings or case studies.

The global consensus meeting, which was organized in December 2020 under the European Society for Medical Oncology, brought together over 80 experts from Europe, North America, and Asia, as well as a patient representative from the EHE Group and Sarcoma Patients EuroNet.

Regarding treatment, complete resection remains the main goal for patients with confirmed unifocal EHE of the soft tissue. Surgery with microscopic negative margins yields an expected cure rate of up to 80%, but individual progression is difficult to predict. Patients with asymptomatic locoregional or systemic metastases and those who are not fit for surgery should be considered for active surveillance.

Although limited data exist for evaluating the role of radiation therapy alone, EHE is thought to be a radiosensitive disease, and radiation can often be combined with surgery based on individual patient considerations such as tumor resectability and risk of recurrence. Other locoregional therapies, such as percutaneous ablation, transarterial chemoembolization, radioembolization, and intense pulsed light therapy, are potential options, but only retrospective data are available on their use as an alternative to surgery and/or radiotherapy.

Regarding systemic treatment, no data have suggested utility with neoadjuvant or adjuvant therapy for patients with localized, resectable EHE. Up-front surveillance is indicated for patients with asymptomatic metastatic disease. However, patients with serosal effusion and/or organ dysfunction should be considered for systemic treatment, but no standard approach has been established. EHE does not appear to be sensitive to conventional chemotherapy, but antitumor activity has been observed retrospectively with treatments including interferon, thalidomide (Thalomid), tyrosine kinase inhibitors, and mTOR inhibitors.

Personalized palliative care, including clinical and psychosocial support, should be considered a critical step in the treatment of patients with EHE, particularly those with symptomatic disease or serosal effusion. Palliative care should be multidisciplinary in nature and involve all relevant specialties to the individual case.

Ultimately, participation in clinical trials is recommended whenever possible, the study authors wrote. Two clinical trials (NCT03331250, NCT03148275) are ongoing in EHE, evaluating eribulin mesylate (Halaven) and trametinib (Mekinist), respectively. Additionally, because clinical trials are likely to be uncontrolled based on the rarity of EHE, patient registries could yield important insight into external controls for these trials.

**REFERENCES**


Sacituzumab Govitecan May Be New Standard of Care in Metastatic TNBC

by JACKIE COLLINS

**Sacituzumab Govitecan-HZIY (Trodelvy) Demonstrated** a significant survival improvement over single-agent chemotherapy treatment of physician’s choice (TPC) for patients with metastatic triple-negative breast cancer (mTNBC), according to data presented by Hope S. Rugo, MD, FASCO.

As part of the OncLive® Rapid Readout video series, which features experts delving into key trial results presented at conferences, Rugo provided her insights on the final analysis data from the international phase 3 ASCENT trial (NCT02574455). The findings were initially presented at the 2021 American Society of Clinical Oncology Annual Meeting.1

In previously published findings, the novel antibody-drug conjugate (ADC) sacituzumab govitecan resulted in a median progression-free survival (PFS) of 5.6 months (95% CI, 4.3-6.3) vs 1.7 months (95% CI, 1.5-2.6) with single-agent TPC (HR, 0.41; 95% CI, 0.32-0.52; P < .001) among patients without brain metastases treated in the study. The median overall survival (OS) with sacituzumab govitecan was 12.1 months (95% CI, 10.7-14.0) vs 6.7 months (95% CI, 5.8-7.7) with single-agent TPC in the overall population (HR, 0.48; 95% CI, 0.38-0.59; P < .001).2

In a subanalysis of the ASCENT study, efficacy outcomes were assessed in the brain metastases-negative population for each individual chemotherapeutic agent. The investigators determined the single-agent chemotherapy before patients were randomized from one of the following choices: eribulin (n = 126), vinorelbine (n = 47), capetitabine (n = 31), or gemcitabine (n = 29).1

According to the subgroup analysis, gemcitabine had the longest median PFS at 2.7 months (95% CI, 1.6-4.8) vs the other single-agent TPCs. Specifically, the median PFS with eribulin was 2.1 months (95% CI, 1.5-2.8), 1.6 months (95% CI, 1.4-2.7) with vinorelbine, and 1.6 months (95% CI, 1.4-2.4) with capetitabine. Further, gemcitabine elicited the longest median OS at 8.4 months (95% CI, 5.0-9.6), vs 6.9 months (95% CI, 5.8-7.8) with eribulin, 5.9 months (95% CI, 4.5-6.7) with vinorelbine, and 5.2 months (95% CI, 3.5-8.6) with capetitabine (Table 1). These data were reported in comparison with a median PFS of 5.6 months (HR, 0.48; 95% CI, 0.38-0.59; P < .001) and a median OS of 12.1 months with sacituzumab govitecan (HR, 0.48; 95% CI, 0.38-0.59; P < .001).

“mTNBC is a disease that has had limited treatment options, and a number of chemotherapy agents are used in sequence,” said Rugo, a professor of medicine and director...
of Breast Oncology and Clinical Trials Education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, and the 2020 Giants of Cancer Care® award winner in the Education category.

“Eribulin has been a commonly used monotherapy for previously treated mTNBC based on data from the EMBRACE trial [NCT00388726], but median PFS in heavily pretreated patients has been poor at less than 3 months.”

“[Sacituzumab govitecan] has become an early standard of care with rapid adoption throughout the United States, where we are treating patients with TNBC and have access to [the agent]. There is tremendous interest around the world for having as quick access to sacituzumab govitecan as possible.”

In April 2021, the FDA approved sacituzumab govitecan for patients with unresectable locally advanced or metastatic TNBC who have received at least 2 prior chemotherapies. One of those therapies could be in the neoadjuvant setting if progression occurred within 12 months. Of the total patient population, 235 and 233 patients were negative for brain metastasis in the sacituzumab govitecan and TPC arms, respectively.1,2

The median age was 54 years (range, 27-82). Forty-two percent of patients had hepatic metastases, 9% had BRCA1/BRCA2 mutations, and 70% had TNBC at diagnosis. Twelve percent had baseline previously treated and stable brain metastases (n = 61; 32 in the sacituzumab govitecan arm, 29 in the TPC arm). Overall, 29% of patients had received prior PD-L1/PD-L1 therapy (Table 2).3,4

Patients were randomized (1:1) to receive sacituzumab govitecan 10 mg as an intravenous infusion on days 1 and 8 of a 21-day cycle or a single-agent TPC. At the data cutoff of March 11, 2020, 15 patients (6%) remained on treatment in the sacituzumab govitecan arm and 0 patients remained on treatment in any TPC agent arm. The most common reason for treatment discontinuation was disease progression.1,2

Additional efficacy end points stratified in the subanalysis were objective response rates (ORRs) and clinical benefit rates (CBRs) for the ADC vs individual chemotherapy.

### Table 1. Efficacy Outcomes in the ASCENT Trial

<table>
<thead>
<tr>
<th></th>
<th>Sacituzumab govitecan (n = 235)</th>
<th>Eribulin (n = 126)</th>
<th>Vinorelbine (n = 47)</th>
<th>Capcitabine (n = 31)</th>
<th>Gemcitabine (n = 29)</th>
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</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
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<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.6 (4.3-6.3)</td>
<td>2.1 (1.5-2.8)</td>
<td>1.6 (1.4-2.7)</td>
<td>1.6 (1.4-2.4)</td>
<td>2.7 (1.6-4.8)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.41 (0.32-0.52), P &lt; .001</td>
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<tr>
<td><strong>OS</strong></td>
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<tr>
<td>Median OS, months (95% CI)</td>
<td>12.1 (10.7-14.0)</td>
<td>6.9 (5.8-7.8)</td>
<td>5.9 (4.5-6.7)</td>
<td>5.2 (3.5-8.6)</td>
<td>8.4 (5.0-9.6)</td>
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<td>HR (95% CI)</td>
<td>0.48 (0.38-0.59), P &lt; .001</td>
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<tr>
<td><strong>ORR</strong></td>
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<tr>
<td>CR (%)</td>
<td>10 (4)</td>
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<td>PR (%)</td>
<td>72 (31)</td>
<td>4 (3)</td>
<td>2 (4)</td>
<td>2 (6)</td>
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<tr>
<td>CBR (%)</td>
<td>105 (45)</td>
<td>10 (8)</td>
<td>3 (6)</td>
<td>3 (10)</td>
<td>4 (14)</td>
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<td>Median DOR, months (95% CI)</td>
<td>6.3 (5.5-9.0)</td>
<td>3.6 (2.9-4.2)</td>
<td>2.8 (NE)</td>
<td>NE</td>
<td>2.9 (NE)</td>
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</table>

CBR, clinical benefit rate; CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TPC, treatment of physician’s choice.

### Table 2. Baseline Characteristics in the ASCENT Trial

<table>
<thead>
<tr>
<th></th>
<th>Sacituzumab govitecan (n = 235)</th>
<th>Eribulin (n = 126)</th>
<th>Vinorelbine (n = 47)</th>
<th>Capcitabine (n = 31)</th>
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<td><strong>Median age, years (range)</strong></td>
<td>54 (29-82)</td>
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<tr>
<td>0</td>
<td>46%</td>
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<td>55%</td>
<td>55%</td>
<td>61%</td>
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<tr>
<td><strong>Number of prior chemotherapies from randomization stratification</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>2-3</td>
<td>71%</td>
<td>78%</td>
<td>40%</td>
<td>87%</td>
<td>69%</td>
</tr>
<tr>
<td>&gt;3</td>
<td>29%</td>
<td>22%</td>
<td>60%</td>
<td>13%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Median prior anticancer regimens (range)</strong></td>
<td>4 (2-17)</td>
<td>4 (2-14)</td>
<td>5 (2-14)</td>
<td>3 (2-7)</td>
<td>5 (2-9)</td>
</tr>
</tbody>
</table>

TPC, treatment of physician’s choice.
IN THE TREATMENT OF **METASTATIC EGFRm NSCLC**

**FIRST-LINE TAGRISSO: TO FIND EVERY ELIGIBLE PATIENT**

**TEST, KNOW, TREAT**

**GIVE ELIGIBLE PATIENTS A CHANCE AT GROUNDBREAKING EFFICACY**

<table>
<thead>
<tr>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>18.9 vs 10.2</strong> months for TAGRISSO vs erlotinib/gefitinib¹</td>
<td><strong>38.6 vs 31.8</strong> months for TAGRISSO vs erlotinib/gefitinib¹</td>
</tr>
<tr>
<td>HR=0.46 (95% CI: 0.37, 0.57); P=0.0001</td>
<td>HR=0.80% (95% CI: 0.64, 1.00); P=0.0462</td>
</tr>
</tbody>
</table>

FLAURA study design: Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFR m NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279, 80 mg orally, once daily) or EGFR-TKI comparator (n=277, gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. Crossover was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included OS, ORR, CNS PFS, and DoR. To provide strong control for the type I error rate, the primary endpoint of PFS and endpoints of OS and CNS PFS were tested sequentially.¹ ¹

**INDICATION**

- TAGRISSO is indicated for the first-line treatment of adult patients with metastatic 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

**IMPORTANT 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
- Heart rate-corrected QT (QTc) interval prolongation occurred in 1% of 1479 TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a QTc >500 msec, and 3.1% of patients had an increase from baseline QTc >60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients. 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist

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IN THE TREATMENT OF METASTATIC EGFRm NSCLC

- TAGRISSO is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer.

- Heart rate-corrected QT (QTc) interval prolongation.

- Interstitial lung disease (ILD)/pneumonitis occurred in patients who develop QTc interval prolongation.

- There are no contraindications for TAGRISSO.

- Withholding TAGRISSO for the type I error rate, the primary endpoint of PFS and endpoints of OS and CNS PFS were tested sequentially.

- Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was progression-free survival (PFS). Withholding TAGRISSO was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with baseline CNS metastases without progression within 12 weeks of starting treatment were allowed to crossover to TAGRISSO.

- Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR-TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. Crossover from the EGFR-TKI comparator to TAGRISSO was not permitted and was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with baseline CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was progression-free survival (PFS). Withholding TAGRISSO was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with baseline CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was progression-free survival (PFS). Withholding TAGRISSO was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation.

- In patients who develop QTc interval prolongation, 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. Withhold TAGRISSO if SJS or major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

- 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.

- References:

Please see Brief Summary of Prescribing Information, including Patient Information on adjacent pages.
TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated as adjuvant therapy after tumor resection in 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 [see Dosage and Administration (2.1) in the full Prescribing Information].

First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC

TAGRISSO is indicated for the first-line treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC as detected by an FDA-approved test, whose disease has progressed or on progressing to second-line TAGRISSO in 15 mL of non-carbonated water, and then use an additional 120 mL (3.25 fluid oz) or ultrasonicate during preparation. Rinse the container with 120 mL of water and immediately drink. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL of water and immediately drink. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL of water and immediately drink. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL of water and immediately drink. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL of water and immediately drink. Do not crush, heat, or ultrasonicate during preparation. 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Do not The following adverse reactions are discussed in greater detail in other sections of the labeling:

• Interstitial Lung Disease/Pneumonitis [see Warnings and Precautions (5.4) in the full Prescribing Information]
• QTc Interval Prolongation [see Warnings and Precautions (5.6) in the full Prescribing Information]

Cardiac adverse reactions included angina, atrial fibrillation, and cardiovascular disorders such as congestive heart failure and myocardial infarction.

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Table 1. Recommended Dosage Modifications for TAGRISSO (cont’d)

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary [see Warnings and Precautions (5.4) in the full Prescribing Information]</td>
<td>Interstitial lung disease (ILD)/Pneumonitis</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

Adverse Reactions
The safety of TAGRISSO was evaluated in ADAURA, a randomized, double-blind, placebot-controlled trial for the adjuvant treatment of patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 16.2 months. Serious adverse reactions were reported in 13% of patients treated with TAGRISSO. The most common serious adverse reaction (>1%) was pneumonia (1.5%). Adverse reactions leading to dose reductions or interruptions occurred in 9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were diarrhea (4.5%), stomatitis (3.9%), rash (1.8%) and rash (1.8%). Adverse reactions leading to permanent discontinuation occurred in 11% of patients treated with TAGRISSO. The most frequent adverse reactions leading to discontinuation of TAGRISSO were interstitial lung disease (2.7%), and rash (1.2%).

Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in ADAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or higher (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>47</td>
<td>2.4</td>
<td>20</td>
<td>0.3</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>1.8</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain**</td>
<td>12</td>
<td>0.3</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>40</td>
<td>0.6</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Nail toxicity§</td>
<td>37</td>
<td>0.9</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Dry skin†</td>
<td>29</td>
<td>0.3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19</td>
<td>0.9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>0.9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous Pain†</td>
<td>18</td>
<td>0.3</td>
<td>25</td>
<td>0.3</td>
</tr>
<tr>
<td>Infection and Infestation Disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>0.6</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract Infection‡</td>
<td>10</td>
<td>0.3</td>
<td>7</td>
<td>0.3</td>
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<tr>
<td>General Disorders and Administration Site Conditions</td>
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</tr>
<tr>
<td>Fatigue†</td>
<td>13</td>
<td>0.6</td>
<td>9</td>
<td>0.3</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness‡</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>0.6</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

§ Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash purpuric, rash pruritic, rash vesicular, rash follicular, erythema, turgidus, acne, dermatitis, dermatitis acroaxial, dry erosion, skin erosion, papulosis.

**Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash purpuric, rash pruritic, rash vesicular, rash follicular, erythema, turgidus, acne, dermatitis, dermatitis acroaxial, dry erosion, skin erosion, papulosis.

† Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash purpuric, rash pruritic, rash vesicular, rash follicular, erythema, turgidus, acne, dermatitis, dermatitis acroaxial, dry erosion, skin erosion, papulosis.

Diabetes, colitis, enterocolitis, enteritis.

‡ Includes abdominal discomfort, abdominal pain, abnormal upper abdomen, abnormal lower pain, abdominal pain, abdominal discomfort, hepatic pain.

§ Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash purpuric, rash pruritic, rash vesicular, rash follicular, erythema, turgidus, acne, dermatitis, dermatitis acroaxial, dry erosion, skin erosion, papulosis.

∆ Includes fatigue, asthenia.

¶ Includes dry skin, skin fissures, xerosis, eczema, xeroderma.

‡ Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychogryphosis, onycholysis, onycholyis, onychomadesis, onychomata, onychorrhexis.

§ Includes pruritus, pruritus generalized, erythral pruritus.

† Includes cough, productive cough, upper-airway cough syndrome.

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

§ Includes pruritus, pruritus generalized, erythral pruritus.

† Includes cough, productive cough, upper-airway cough syndrome.

<table>
<thead>
<tr>
<th>Laboratory Abnormality*</th>
<th>All Grades (%)</th>
<th>Grade 3 or higher (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
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<td></td>
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<tr>
<td>Leukopenia</td>
<td>54</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>47</td>
<td>0</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>Anemia</td>
<td>44</td>
<td>2.4</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30</td>
<td>0.3</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25</td>
<td>2.3</td>
<td>30</td>
<td>0.9</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>24</td>
<td>1.3</td>
<td>14</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Hyperglycemia is based on the number of patients who had follow-up laboratory data. Laboratory abnormalities in ADAURA that occurred in ≥1% of patients receiving TAGRISSO was increased blood creatinine (10%).

Previously Untreated EGFR-Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active-controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. Serious adverse reactions were reported in 4% of patients treated with TAGRISSO, the most common serious adverse reactions (≥1%) were pneumonia (2.9%), skin disorder (2.1%), and prolongation of QT interval (1.8%). 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 (3.4%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/Pneumonitis (0.3%).

Table 5. Laboratory Abnormalities Occurring in ≥10% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or higher (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>53</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>47</td>
<td>0</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>Anemia</td>
<td>44</td>
<td>2.4</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>0.3</td>
<td>7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Clinical relevant adverse reactions in FLAURA in <10% of patients receiving TAGRISSO were alopecia (7%), epistaxis (6%), interstitial lung disease (3%), palmar-plantar erythrodysesthesia syndrome (1.8%), urticaria (1.5%), keratitis (0.6%), QTc interval prolongation (0.6%), and erythema multiform (0.3%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TARGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
<th>Placebo (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12</td>
<td>0.4</td>
<td>7</td>
</tr>
</tbody>
</table>
therapy-treated patients. The trial population characteristics were: median age 64 years, age less than 65 (55%), female (64%), Asian (65%), never smokers (68%), and EGFR PS 0 or 1 (100%).

Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 26% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis).

Dose reductions occurred in 29% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neutropenia (1.1%), and diastolic (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (2%).

Tables 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy/Pemetrexed/Cisplatin (N=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>41 (14.6)</td>
<td>27 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (5.8)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>19 (6.9)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (5.1)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (4.0)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>34 (12.2)</td>
<td>16 (5.9)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (8.3)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>22 (8.0)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (4.7)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>General Disorders and Admissions Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17 (6.1)</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (3.6)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18 (6.5)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive Dystonia</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>
| Adverse Reactions in AURAs in >10% of patients receiving TAGRISSO were epistaxis (5%), alopecia (3.6%), urticaria (2.9%), palmar-plantar erythrodysaesthesia syndrome (1.8%), QT interval prolongation (1.4%), keratitis (1.1%), and erythema multiforme (0.7%). QT interval prolongation represents the incidence of patients who had a QTcF of 0.5 seconds or more.

### Table 7. Laboratory Abnormalities Worsening from Baseline in >20% of Patients in AURAs

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy/Pemetrexed/Cisplatin (N=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43 (15.2)</td>
<td>29 (10.7)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 (22.8)</td>
<td>51 (18.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 (16.5)</td>
<td>33 (12.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 (9.7)</td>
<td>23 (8.5)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9 (3.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26 (9.3)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>20 (7.2)</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>12 (4.3)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>9 (3.3)</td>
<td>3 (1.1)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
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<td>6 (2.2)</td>
</tr>
<tr>
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</table>

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

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<thead>
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</table>
regimens. The ORR with sacituzumab govitecan was 35%, vs 5%, 4%, 0%, and 3% with eribulin, vinorelbine, capectabine, or gemcitabine, respectively. Ten patients in the sacituzumab govitecan arm had a complete response vs 2 patients in the eribulin arm; no patients achieved a complete response in the other chemotherapy groups. The median duration of response for the sacituzumab govitecan group was 6.3 months and ranged from 2.8 to 3.6 months for the TPC groups.

The CBR with sacituzumab govitecan was 45%, vs 8%, 6%, 10%, and 14% with eribulin, vinorelbine, capectabine, or gemcitabine, respectively. CBR was defined as the percentage of patients with a confirmed best overall response of complete response or partial response, and stable disease greater than 6 months.

Thus, Rugo highlighted the fact that none of the agents individually tested in the TPC arm did not offer any significant outcomes when directly compared against sacituzumab govitecan.

“You can see the big separation and how similar the TPC arms fall in their [Kaplan-Meier] curves,” Rugo said. “[Also, ORR] was extremely low for the agents and they were all very similar so one did not stand out.”

Regarding safety, the investigators reported a number of grade 3/4 treatment-related adverse effects (AEs) observed in the safety population with sacituzumab govitecan (n = 258) vs eribulin (n = 123), respectively. These included neutropenia (51% vs 31%), leukopenia (10% vs 5%), diarrhea (10% vs 0%), anemia (8% vs 2%), febrile neutropenia (6% vs 2%), fatigue (3% vs 5%), and peripheral neuropathy (0% vs 2%).

Additionally, grade 3/4 AEs with sacituzumab govitecan vs a pooled analysis of patients treated with vinorelbine, capectabine, and gemcitabine (n = 101) included neutropenia (51% vs 36%), leukopenia (10% vs 6%), diarrhea (10% vs 1%), anemia (8% vs 8%), febrile neutropenia (6% vs 2%), and fatigue (3% vs 6%).

Discontinuation rates because of AEs for sacituzumab govitecan, eribulin, vinorelbine, capectabine, and gemcitabine were 5%, 2%, 10%, 7%, and 9%, respectively. One treatment-related death was reported in the TPC arm (eribulin; neutropenic sepsis).

“What we learned supports what we understood from the parent ASCENT trial and shows how effective sacituzumab govitecan is compared with TPCs, but it also gave us important additional information about safety management,” Rugo said. “The more we look at safety and think about prospective management of safety, the better we can help our patients stay on effective therapy and also retain quality of life.”

In an analysis of health-related quality-of-life (HRQOL) data presented at the European Society for Medical Oncology Annual Congress 2021, sacituzumab govitecan showed statistically significant and clinically meaningful improvements over TPC.

Specifically, the agent prolonged time to first deterioration of in nearly all HRQOL domains and significantly shortened the time to improvement in physical functioning and pain. The median time to first clinically meaningful deterioration for physical functioning was 22.1 weeks with sacituzumab govitecan vs 12.1 weeks with TPC (HR, 0.61; 95% CI, 0.49-0.75). For pain the median time to deterioration was 21.6 weeks vs 9.9 weeks with TPC (HR, 0.48; 95% CI, 0.48-0.74).

The benefit extended to other HRQOL domains including fatigue and role functioning; however, the median time to deterioration in the global health status and quality of life domain for those treated with TPC at 15.1 weeks compared with 14.1 weeks with sacituzumab govitecan (HR, 0.87; 95% CI, 0.70-1.07). In her discussion of the subgroup analysis Rugo concluded that sacituzumab govitecan should be considered as a new standard of care in patients with pretreated mTNBC. She added that ongoing clinical trials are evaluating moving sacituzumab govitecan into the first-line setting as well as the postneoadjuvant and neoadjuvant settings.

“There are also clinical trials evaluating sacituzumab govitecan in combination with checkpoint inhibitors,” Rugo noted. “There’s great interest in capitalizing on those potential immune effects of ADCs [with] these combinations.”

REFERENCES


New Class of Radiopharmaceutical Therapy Makes Headway in Prostate Cancer

by JANE DE LARTIGUE, PhD

INVESTIGATORS HAVE MADE GREAT strides in the development of radiopharmaceuticals for prostate cancer diagnostics, culminating in recent FDA approvals for the first prostate-specific membrane antigen (PSMA)-targeted radioligands, gallium 68 (68Ga)-PSMA-11 and piflufolastat F 18 (Pylarify), for the detection of disease recurrence and metastatic lesions.1,2

Meanwhile, the use of PSMA-targeted radiopharmaceuticals for prostate cancer therapy is heading for the mainstream treatment landscape. Positive results from the phase 3 VISION trial (NCT03511664) involving lutetium 177 (177Lu)-PSMA-617, a radiolabeled small molecule inhibitor of PSMA, were recently published and could be used to support FDA approval for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).3,4

A number of other PSMA-targeted radioligands are undergoing clinical evaluation, including several that incorporate monoclonal antibodies (mAbs) rather than small molecule inhibitors (TABLE). The 2 types of agents have distinct pharmacokinetic, safety, and efficacy profiles that could lend themselves to different patient populations.5,6

To date, clinical development has been focused on conjugating PSMA-targeted drugs to beta-emitting radioisotopes, but alpha emitters could offer greater efficacy if the challenge of increased toxicity can be addressed.7 Early clinical data for alpha emitters such as actinium 225 (225Ac)-labeled small molecule inhibitors and mAbs demonstrate promising results, including in tandem therapy with 177Lu-PSMA-617.6,8,9

TARGETED RADIOACTIVE TRACERS

Radiopharmaceuticals are systemically delivered radioactive isotopes or compounds that localize to tumors—via either physiologic mechanisms or incorporation of a specific targeting molecule—while sparing normal tissues. They can be used as tracers, facilitating tumor detection via diagnostic imaging using PET/CT or other imaging technologies that detect the radiation (often in the form of positrons) emitted by the radioisotopes. Alternatively, radiopharmaceuticals can be designed to enter cancer cells and induce cytotoxic DNA damage for therapeutic purposes.6,10,11

In the diagnostic field, much of the recent attention has centered on radiopharmaceuticals targeting PSMA, a cell membrane protein expressed at particularly high levels on prostate cancer cells.2,11 Administered intravenously, PSMA-targeted radiolabeled tracers accumulate at tumor sites with high levels of PSMA expression.11

PSMA-targeted radiotracers have progressed rapidly through clinical trials.8 In December 2020, 68Ga-PSMA-11 became the first PSMA-targeted radiopharmaceutical approved for PET imaging purposes in patients with prostate cancer. Specifically, 68Ga-PSMA-11 can be used to help confirm suspected prostate cancer recurrence based on elevated prostate-specific antigen (PSA) levels or to detect metastatic lesions.1

In May 2021, 68Ga-PSMA-11 was joined by a second PET imaging agent, piflufolastat F 18, a small molecule targeting PSMA conjugated to a fluorine 18 isotope.2 Piflufolastat F 18 was approved for the same indications that 68Ga-PSMA-11 has.2 However, the FDA approved 68Ga-PSMA-11 for use at 2 academic sites—the University of California, Los Angeles and the University of California, San Francisco—whereas piflufolastat F 18 is expected to be more widely available throughout the United States.2,12

If detected early, recurrent disease can be managed effectively with salvage therapy, and accurate detection of metastatic lesions can help spare patients unnecessary surgery. Current PET/CT tracers for prostate cancer imaging have limited ability to detect recurrent disease in a timely manner and identify occult metastases. Thus, the introduction of PSMA-targeted tracers is revolutionizing prostate cancer imaging and detection.7

RADIOPHARMACEUTICAL THERAPIES

The development of radiopharmaceutical therapies has also progressed rapidly in recent years. Although the current market for such therapeutics is estimated at approximately one-third the size of the imaging market, the uptake is expected to grow substantially over the next several years.13 The category, sometimes called radiotheranostics, broadly comprises beta- and alpha-emitting radiation therapy and brachytherapy.3,13

The concept of leveraging radioisotopes for cancer therapy has been explored for more than 70 years, notably through the use of radioactive iodine for thyroid cancer.1 Two beta-emitting agents, strontium-89 chloride (Metastron) and samarium-153 (Quadramet), have been FDA approved since the 1990s for palliating painful bone metastases and are used in this setting for patients with prostate cancer.5,14

In 2013, the FDA approved radium-223 dichloride (Xofigo), an alpha-emitting radiopharmaceutical, for the treatment of patients with castration-resistant prostate cancer with...
symptomatic bone metastases and no known visceral metastatic disease. Experts anticipate that a new generation of therapeutic radioisotopes in development will expand therapeutic efficacy of these agents, particularly for more prevalent tumor types.\textsuperscript{3,15}

The new crop of agents includes \textsuperscript{177}Lu-dotatate (Lutathera), a radiolabeled somatostatin analogue that the FDA approved in January 2018 for the treatment of patients with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors.\textsuperscript{16} However, \textsuperscript{177}Lu-dotatate occupies a small niche market, whereas PSMA-targeted radioligand therapy (RLT), which is designed to treat patients with prostate cancer, the second-leading cause of cancer-related mortality in men in the United States,\textsuperscript{17} has brought much greater attention to the field of radiopharmaceutical therapy.\textsuperscript{15}

\section*{The Network}

\textbf{PSMA: An Antigen of Opportunity}

by JANE DE LARTIGUE, PhD

\textbf{PROSTATE-SPECIFIC MEMBRANE ANTIGEN} (PSMA), a glycoprotein comprising 750 amino acids with multiple antigenic epitopes, has emerged as an attractive diagnostic and therapeutic target in prostate cancer since its discovery in 1987.\textsuperscript{1}

PSMA is a membrane-bound protein, not to be confused with another clinically relevant molecule, prostate-specific antigen, which is a secreted enzyme found in the bloodstream.\textsuperscript{2} More specifically, PSMA is a type II transmembrane protein: It passes across the cell membrane only once and has its N-terminus inside the cell and its C-terminus protruding from the cell.\textsuperscript{3-5}

In healthy prostate tissue, PSMA is typically expressed on the cytoplasmic and apical side of the epithelium surrounding the prostatic ducts, whereas in cancerous tissue it relocates to the luminal surface.\textsuperscript{2} Despite its name, PSMA expression is not limited to prostate cells; low levels are found in a number of different tissues, including the kidney, salivary and lacrimal glands, brain, and intestines.\textsuperscript{3-5}

Broadly speaking, PSMA is an enzyme, and its function depends on the type of tissue in which it is expressed but includes a role in folate metabolism. Its precise role in the prostate is currently unknown.\textsuperscript{3,7,8}

Several factors make PSMA a highly sought-after target in prostate cancer therapy. Although prostate expression of PSMA is not exclusive to malignant cells, PSMA is particularly highly expressed in almost all prostate cancers,\textsuperscript{5,7} with an estimated 100- to 1000-fold higher expression on prostate cancer cells compared with benign prostate tissue.\textsuperscript{3}

Furthermore, expression of PSMA has been shown to increase as prostate cancer progresses, with higher levels of expression found in higher-grade and metastatic tumors, although there is significant heterogeneity between tumors. The degree of PSMA expression also seems to correlate with patient prognosis.\textsuperscript{5,7,9}

Another attractive feature of PSMA as a target is that it is rapidly internalized in endosomal complexes upon therapeutic ligand binding, which means that any PSMA-targeting drug could also be taken up into a PSMA-expressing cell.\textsuperscript{2,7}

Radiolabeled PSMA ligands represent one such pharmaceutical approach exploiting these attributes of PSMA for imaging and treatment of prostate cancer (\textbf{FIGURE}1). Conjugating radioactive isotopes to PSMA-targeted drugs enables targeted delivery of radioactivity inside prostate cancer cells that, depending on the specific radioactive isotope used, either aids visualization of PSMA-positive prostate cancer lesions on a scan or induces cancer cell death.\textsuperscript{1,6}

Other therapeutic strategies include antibody-drug conjugates, chimeric antigen receptor T-cell therapy, photodynamic therapy, and imaging-guided surgery.\textsuperscript{1}

\begin{figure}[th]
\centering
\includegraphics[width=\textwidth]{binding_sites.png}
\caption{Binding Sites for Radiopharmaceutical Therapy in Prostate Cancer\textsuperscript{7}}
\end{figure}

Investigators have identified several binding sites for therapies directed at prostate-specific member antigen (PSMA), a glycoprotein highly expressed in most prostate cancers. Radiolabeled antibodies and small molecules are leading therapeutic strategies directed at PSMA.\textsuperscript{1}


For a full list of references, see the article at \textsuperscript{1}
PSMA-targeting small molecule inhibitors and mAbs are conjugated to different radioisotopes for therapeutic purposes, most commonly $^{177}$Lu, which emits beta radiation. At the forefront of clinical development are the radiolabeled inhibitors $^{177}$Lu-PSMA-617 and $^{225}$Ac-PSMA-617.

Research groups in Germany initially developed both therapies. Endocyte subsequently purchased the rights to $^{177}$Lu-PSMA-617, and Novartis, which acquired Endocyte in 2018, is now developing $^{177}$Lu-PSMA-I&T.

Findings from multiple studies in small cohorts of patients with mCRPC have demonstrated that treatment with $^{177}$Lu-PSMA-617 or $^{177}$Lu-PSMA-I&T resulted in significant declines in PSA levels. In terms of pharmacokinetics, $^{177}$Lu-PSMA-617 is favored because of its lower kidney uptake, but no head-to-head comparisons of the 2 agents have been performed to date.

Results from the first prospective trial (LuPSMA; Australian New Zealand Clinical Trials Registry number 12615000912583) of $^{177}$Lu-PSMA-617 in 30 patients with mCRPC demonstrated a PSA response in more than half of the participants, with response defined according to Prostate Cancer Clinical Trial Working Group criteria as a PSA decline from baseline of 50% or greater. The most common treatment-related adverse events (TRAEs) were dry mouth, nausea, and fatigue. Grade 3/4 TRAEs included lymphocytopenia (37%) and anemia (13%) each; however, investigators described the overall rate of grade 3/4 hematologic toxicity as low and comparable to previously published retrospective data.

In the phase 2 TherAP trial (NCT03392428), $^{177}$Lu-PSMA-617 administered at 6 to 8.5 GBq every 6 weeks for up to 6 cycles was compared with cabazitaxel (Jevtana) given at 20 mg/m2 every 3 weeks for up to 10 cycles. Among 183 patients with mCRPC, the RLT resulted in a higher PSA response rate (66% vs 37%; difference, 29%; 95% CI, 16%-42%; P < .0001) and a lower rate of grade 3/4 AEs (33% vs 53%), respectively.

Investigators have published topline data from the international, randomized, phase 3 VISION trial comparing $^{177}$Lu-PSMA-617 (7.4 GBq every 6 weeks for 4-6 cycles) plus standard of care (SOC; excluding cabazitaxel) vs SOC alone in patients with mCRPC.

Outcomes from 581 patients were reported in the analysis set after a median follow-up of 20.3 months (95% CI, 19.8-21.0 months) in the $^{177}$Lu-PSMA-617 arm and 19.8 months (95% CI, 18.3-20.8 months) in the control group. Treatment with the RLT significantly delayed progression, with the median imaging-based progression-free survival (PFS) of 8.7 months compared with 3.4 months for SOC (HR, 0.40; 99.2% CI, 0.29-0.57; P < .0001).

Among 831 patients who underwent randomization, the median overall survival (OS) was 15.3 months for patients treated with $^{177}$Lu-PSMA-617 plus SOC vs 11.3 months for those treated with SOC alone (HR, 0.62; 95% CI, 0.52-0.74; P < .001).

Fatigue, dry mouth, and nausea were the most common AEs in the $^{177}$Lu-PSMA-617 arm; grade 3 and higher AEs, predominantly hematologic toxicities, also were more common with the RLT.

In June 2021, the FDA awarded $^{177}$Lu-PSMA-617 a breakthrough therapy designation on the basis of these results. Ongoing studies are examining the agent in patients with chemotherapy-naïve mCRPC or hormone-sensitive prostate cancer.

Meanwhile, ongoing clinical development of radiolabeled PSMA inhibitors focuses on further improving safety and efficacy. One strategy involves adding an albumin-binding domain to the RLT to enhance circulation time and increase tumor uptake.
Targeted Technology is developing one such drug, $^{177}$Lu-DOTA-N3-CTT1403.\textsuperscript{11,22}

**PSMA ANTIBODIES**

Although the focus has been on small molecule PSMA inhibitors, several radiolabeled antibodies, which have different characteristics that can affect efficacy and safety, also are in development. Antibodies are larger and more challenging to synthesize, and they have a longer half-life in the circulation.\textsuperscript{5,6}

Antibody therapy tends to lead to more off-target toxicity in the bone marrow and liver, whereas small molecule inhibitors have more on-target toxicity in other tissues where PSMA is expressed, including the kidney, salivary glands, and small intestine. The major toxicities associated with $^{227}$Lu-PSMA-617 are dry mouth and nausea, whereas hematologic toxicities are more common with PSMA antibody-based radiopharmaceuticals.\textsuperscript{5,23}

$^{177}$Lu conjugated to the PSMA-targeted mAb J591 has demonstrated efficacy in early-phase clinical trials in patients with prostate cancer, albeit with dose-limiting myelosuppression. In findings from a phase 1/2 study (NCT00538668), fractionated dosing permitted higher cumulative doses of $^{177}$Lu-J591 to be administered, with higher doses correlated with increases in both efficacy and toxicity. Myelosuppression was generally predictable, short-term, and self-limiting.\textsuperscript{24,25}

Telix Pharmaceuticals is developing TLX591 ($^{177}$Lu-DOTA-rosopatamab), which employs an enhanced version of the J591 antibody, rosopatamab, conjugated to $^{177}$Lu. The therapy has been engineered to have a shorter plasma half-life, which is expected to reduce hematologic toxicity while maintaining antitumor efficacy.\textsuperscript{26} TLX391 is scheduled to be evaluated as a second-line treatment for patients with mCRPC that expresses PSMA in the phase 3 PROSTACT trial (NCT04876651).\textsuperscript{26}

**ALPHA EMITTERS**

Another strategy to increase the efficacy of RLT is to use alpha radiation-emitting isotopes, such as $^{225}$Ac. These have several potential advantages, including higher energy and lower cell penetration. The former increases the probability of inducing double-stranded breaks in the DNA of target cells, and the latter helps localize their cytotoxic activity to the tumor.\textsuperscript{6,15}

Radium 223, the only alpha-emitting radiopharmaceutical approved for prostate cancer, is a calcium mimic that naturally accumulates in areas of high bone turnover. It is approved for the treatment of patients with symptomatic bone metastases but has no efficacy against extraskeletal metastases.\textsuperscript{6,13}

A number of clinical studies of $^{225}$Ac-PSMA-617, an alpha emitter that Novartis also is developing, have demonstrated significant antitumor efficacy but at the cost of increased toxicity. Dry mouth is a particularly common AE that can significantly reduce quality of life and is a leading cause of treatment discontinuation.\textsuperscript{27-30}

Several strategies to reduce the risk of toxicity are being tested. These include dynamic de-escalation, wherein a fixed dose of 8 MBq is used in the first cycle and then reduced in subsequent cycles in patients with a good response.

Another approach being explored is tandem RLT combining $^{177}$Lu-PSMA-617 with $^{225}$Ac-PSMA-617, which could augment the efficacy of the former while mitigating the toxicity of the latter. In a retrospective study of $^{177}$Lu-naïve patients with a poor prognosis (N = 15) who received treatment within a prospective patient registry (REALITY Study; NCT04833517), tandem therapy resulted in biochemical partial remission in 53.3% of patients, a median PFS of 9.1 months (defined by PSA progression), and a median OS of 14.8 months. The only grade 3/4 toxicities were 2 cases of grade 3 anemia.\textsuperscript{8}

The use of PSMA-targeted mAbs as opposed to small molecule inhibitors also could help reduce AEs because mAbs have less on-target toxicity in nontumor tissues such as salivary glands. Initial findings from an ongoing phase 1 trial (NCT03276572) showed that treatment with $^{225}$Ac-J591 at 7 dose levels between 13.3 and 93.3 kBq/kg resulted in a PSA response in 35% of 22 patients and just 1 grade 3/4 TRAE.\textsuperscript{9}

Telix Pharmaceuticals is developing TLX592, known as $^{225}$Ac-TLX592 and $^{64}$Cu-DOTA-TLX592, a next-generation PSMA-targeted mAb optimized for use as a $^{225}$Ac-immunoconjugate. Because alpha radiation cannot be detected with PET, investigators are performing preliminary examination of the biological properties of TLX592 using a copper 64–conjugated version in the first-in-human CUPID trial (NCT04726033), which recently began enrolling patients. Copper 64 will be substituted with $^{227}$Th when therapeutic dosing of participants begins.\textsuperscript{31}

Finally, some investigators are using a third alpha-emitting radioisotope, thorium 227 ($^{227}$Th), in RLT. BAY 2315497 is a $^{227}$Th-conjugated PSMA-targeted mAb.\textsuperscript{32}

A phase 1 clinical trial of this drug is ongoing (NCT03724747).

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Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.
ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status.¹⁻⁴

**Indication**

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

**Important Safety Information**

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

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

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

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

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

**References:**


 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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Produced in USA.
Do not start ZEJULA until patients have recovered from hematological toxicity. In NOVA, ≥Grade 3 thrombocytopenia, anemia, and neutropenia were noted. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 5% of patients receiving ZEJULA 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 NOVA, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% 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). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRA, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% 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 ZEJULA. 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 ZEJULA, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).

5.4 Posterior Reversible Encephalopathy Syndrome

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

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

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman (see Preclinical/Pathologic (12.1) of full prescribing information). ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets active 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.

Advise 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 ZEJULA (see Use in Specific Populations (8.1, 8.3)).

5.6 Allergic Reactions to FB&CC Yellow No. 5 (Tartrazine)

ZEJULA capsules contain FB&CC Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FB&CC Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin 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 (5.5))
- 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 ZEJULA in the pooled PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (65%), anemia (56%), fatigue (52%), decreased appetite (39%), vomiting (33%), abdominal pain (36%), and decreased weight (35%).

The most common adverse reactions of all grades in >5% and ≥Grade 3 are shown in Tables 1 and 2.

Table 1: Adverse Reactions Occurring in ≥20% of Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Blood and lymphoid system disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
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</tbody>
</table>

Neutropenia b 36 8 15 1

Leukopenia a 42 8 21 1

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Nausea 57 28 1 1

Constipation 40 20 1 0

Vomiting 22 12 1 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
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</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
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</tbody>
</table>

Fatigue 51 41 3 1

Investigations

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

AST/ALT elevation 4 7 3 0

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Decreased appetite 19 8 1 0

Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Musculoskeletal pain 39 38 1 0

Nervous system disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Headache 26 15 0.4 0

Dizziness 19 13 0 0

Psychiatric disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Insomnia 25 15 1 0

Renal and urinary disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Acute kidney injury 12 5 0.2 0

Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Dyspnea 22 13 0.4 1

Cough 18 15 0 0.4

Vascular disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
<td>Placebo (n=169)</td>
</tr>
</tbody>
</table>

Hypertension 18 7 6 1

AST/ALT: Aspartate transaminase/alanine aminotransferase

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

†Common Terminology Criteria for Adverse Events version 4.02.
Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA: Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11.2 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >/=2% of patients were anemia (8%), fever (7%), and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >/=2% of patients who received ZEJULA included thrombocytopenia and anemia (5% each) and nausea (2.4%). Adverse reactions to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (%n=86)</th>
<th>Placebo (%n=367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4% 54/86</td>
<td>1% 3/367</td>
</tr>
<tr>
<td>Anemia</td>
<td>5% 44/86</td>
<td>1% 13/367</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1% 4/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3% 12/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4% 3/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Constipation</td>
<td>1% 3/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2% 2/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4% 3/86</td>
<td>2% 7/367</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1% 1/86</td>
<td>0% 0/367</td>
</tr>
</tbody>
</table>

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

*Common Terminology Criteria for Adverse Events version 4.02.*

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (%n=86)</th>
<th>Placebo (%n=367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>4% 4/86</td>
<td>1% 3/367</td>
</tr>
<tr>
<td>Anemia</td>
<td>2% 2/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2% 2/86</td>
<td>0% 0/367</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2% 2/86</td>
<td>0% 0/367</td>
</tr>
</tbody>
</table>

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

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (%n=367)</th>
<th>Placebo (%n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>4% 15/367</td>
<td>1% 2/179</td>
</tr>
<tr>
<td>Anemia</td>
<td>2% 8/367</td>
<td>0% 0/179</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2% 8/367</td>
<td>0% 0/179</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2% 8/367</td>
<td>0% 0/179</td>
</tr>
</tbody>
</table>

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

Niraparib may cause aplastic anemia and thrombocytopenia.

Increased gamma-glutamyltransferase was reported in 40% of patients treated with niraparib

Table 6. Abnormal Laboratory Findings in >25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83</td>
<td>26</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman. No data are available regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e., g., bone marrow) [see Warnings and Precautions (5.5)].

Inform patients on how to take ZEJULA

Advise females to use effective contraception following treatment with ZEJULA and for at least 6 months after receiving the last dose.

Females: Avoid use of hormonal or nonhormonal methods of effective contraception following treatment with ZEJULA and for at least 6 months after receiving the last dose.

Infertility

Females: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (5.1.3) 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]. Monitor patients for hematologic toxicity and reduce the dose further, if needed [see Dosage and Administration (2.3) of full prescribing information].

For patients with mild hepatic impairment (total bilirubin <1.5 x ULN and any AST level or bilirubin <1.5 x ULN and any AST level) [see Clinical Pharmacology (12.3) of full prescribing information].

17 PATIENT COUNSELING INFORMATION

Inform patients on how to take ZEJULA [see Dosage and Administration (2.2) of full prescribing information].

Advise patients to take ZEJULA as directed.

Dosing Instructions

Inform patients on how to take ZEJULA

Advise females to report any signs or symptoms indicating pregnancy or potential loss of the pregnancy

Embryo-Fetal Toxicity

Advise females to report any signs or symptoms indicating pregnancy or potential loss of the pregnancy

Nonclinical Toxicology

Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (5.1.3) of full prescribing information].

Infertility

Females: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (5.1.3) of full prescribing information].
CLINICAL ADVANCES IN THE treatment of small cell lung cancer (SCLC) have lagged behind those of other tumor types, but the delay is not for lack of effort. In recent years, however, improved understanding of disease biology has identified some novel targets that may make these tumors more vulnerable to treatment. One such approach in the frontline setting has been the integration of various immune checkpoint inhibitors into chemotherapy regimens, whereas in the second-line setting, a new chemotherapy agent has recently been added to the treatment armamentarium.

During a recent OncLive Peer Exchange®, a panel of thoracic cancer experts discussed the latest developments in treating patients with SCLC in both the first- and second-line settings. They examined the clinical trial data for some newer agents, including some reassuring real-world data, and discussed how they use these agents in clinical practice.

IMMUNE CHECKPOINT INHIBITORS IN THE FIRST LINE
Two immune checkpoint inhibitors are FDA approved for use in combination with chemotherapy in treatment-naïve patients with extensive-stage SCLC: atezolizumab (Tecentriq) and durvalumab (Imfinzi). A third agent, pembrolizumab (Keytruda), was explored in the KEYNOTE-604 trial (NCT03066778) but did not meet the prespecified significance threshold for overall survival (OS).

Atezolizumab
The FDA approved atezolizumab in March 2019 based on data from the phase 3 IMpower133 trial (NCT02763579). IMpower133 was the first major change to frontline treatment for extensive-stage SCLC in 30 or 40 years. [It] showed that adding the PD-L1 inhibitor atezolizumab concurrently with chemotherapy and as maintenance treatment to carboplatin-etoposide chemotherapy improved both progression-free survival (PFS) and OS without adding notable toxicity, Stephen V. Liu, MD, said. He explained that although chemotherapy alone with platinum-etoposide provided reliably high response rates, it was also associated with high relapse rates and a short PFS and OS, spurring the search for better standards of care.

IMpower133 randomly assigned 403 treatment-naïve patients with extensive-stage SCLC to receive carboplatin and etoposide with either atezolizumab (n = 201) or placebo (n = 202). The combination showed benefit in OS and PFS after a median follow-up of 13.9 months, which was maintained with data from a median follow-up of 22.9 months (TABLE 1). “When we look at the curves, we see that they separate,” Liu said. “It’s not the degree of benefit we are all waiting for, but it’s clearly an improvement over chemotherapy alone. We are trying to identify the patients who derive benefit.” He noted that biomarker studies...
have thus far failed to show which patients are most likely to benefit from the addition of atezolizumab, with factors such as tumor mutational burden (TMB) and PD-L1 expression not found to be useful. Although Liu noted that patients with more inflammatory disease have shown enriched benefit with atezolizumab, this finding does not guide who should and should not receive this treatment.

Whereas biomarker studies have been somewhat disappointing, recent real-world data have been exciting. Liu discussed some real-world data for atezolizumab presented at the 2021 American Society of Clinical Oncology Annual Meeting. The data come from a retrospective review of The US Oncology Network electronic health records for adults with extensive-stage SCLC who received a diagnosis between October 2018 and December 2019, with follow-up through the end of March 2020. Of the 347 patients included in the study, 77% received atezolizumab. Liu said this shows a very broad uptake of the atezolizumab regimen in clinical practice. More importantly, despite the patients being much older and more diverse having more brain metastases compared with the IMpower133 population, outcomes were similar, with treatment duration, continued therapy, and marked survival being almost identical between the clinical trial and real-world cohorts, Liu explained.

“I love those real-world data because it’s a completely different patient population from what we get in clinical trials. We all realize that in the real world, that’s what we have, [so] it’s very comforting and good to see that the results seem to match what we got in the clinical trial in terms of the clinical efficacy,” Hossein Borghaei, DO, MS, said.

### Durvalumab

The FDA approved durvalumab in March 2020 based on data from the phase 3 CASPIAN trial (NCT03043872). The CASPIAN trial included 805 treatment-naïve patients with extensive-stage SCLC who were randomly assigned 1:1:1 to durvalumab plus platinum-etoposide (n = 268), durvalumab plus tremelimumab plus platinum-etoposide (n = 268), or platinum-etoposide alone (n = 269). Interim analysis comparing results for durvalumab plus platinum-etoposide with platinum-etoposide alone showed significant benefit with the addition of durvalumab, with a median OS of 13.0 months (95% CI, 11.5-14.8) vs 10.3 months (95% CI, 9.3-11.2) in these treatment arms, respectively, (HR, 0.73; 95% CI, 0.59-0.91; P = .0047). At 18 months, 34% (95% CI, 26.9%-41.0%) of patients in the durvalumab arm were alive compared with 25% (95% CI, 18.4%-31.6%) in the chemotherapy-alone arm. “It’s very similar to the atezolizumab data, which made everybody feel a little better,” Anne Chiang, MD, PhD, said.

Chiang explained that although CASPIAN was similar in design to IMpower133, it had some distinguishing features. She noted that patients could be treated with cisplatin or carboplatin per investigator’s choice and that the trial included patients with asymptomatic brain metastases, including those previously treated with prophylactic cranial irradiation. The trial also included a third arm, which added the anti–CTLA-4 monoclonal antibody tremelimumab to durvalumab plus platinum-etoposide. She noted that the data for this arm were not positive, with a median follow-up of 25.1 months showing a median OS of a little over 10 months in both the tremelimumab and chemotherapy-alone arms.

“Although there wasn’t a difference in OS [with the addition of tremelimumab], if you look at 12 months out at the landmark analysis, or even 24 months out, there are a significant number of patients surviving,” Chiang said, noting it is approximately 20% of all durvalumab-treated patients vs 5% of those treated with only chemotherapy. Furthermore, characterization of long-term clinical benefit in treatment responders suggests those who achieve a PFS of at least 12 months have exceptional 2-year OS rates greater than 75%, with patients receiving durvalumab more than 3 times as likely to derive long-term benefit. That’s saying if you’re going to do well, you’re going to do really well,” Chiang said.

As with atezolizumab, TMB has not been found to be predictive of response to durvalumab treatment. “Whether or not you used a cut point of 10 or 16 mutations per megabase, that wasn’t predictive of response. TMB is not the marker here,” Chiang said.

### Practical Perspectives on Chemotherapy-Immunotherapy

“For the most part, [I use] chemotherapy-immunotherapy for all patients,” Wade T. Iams, MD, said. He explained that a growing body of evidence suggests chemotherapy-immunotherapy can be safely used in most patients, including those previously thought to be ineligible, such as those with underlying autoimmune diseases, provided they are closely monitored for immune-related adverse effects (AEs). The only time he would not pursue this approach, Iams said, is in the setting of a severe underlying autoimmune disease with visceral organ damage requiring more than 10 mg of systemic glucocorticoids daily for maintenance. As for selecting between available checkpoint inhibitors, Iams said he “approach[es] atezolizumab and durvalumab as equivalent.”

When asked about the chemotherapy component of first-line SCLC treatment, Chiang said

### TABLE 1. Follow-up Data From IMpower 133

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Atezolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.9 months</td>
<td>12.3 (10.8-15.9)</td>
<td>10.3 (9.3-11.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.70 (0.54-0.91); P = .007</td>
<td>0.76 (0.60-0.95); descriptive P = .0154</td>
</tr>
<tr>
<td>22.9 months</td>
<td>12.3 (10.8-15.8)</td>
<td>10.3 (9.3-11.3)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>5.2 (4.4-5.6)</td>
<td>4.3 (4.2-4.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.77 (0.62-0.96); P = .02</td>
<td>0.77 (0.63-0.95)</td>
</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival.
she usually uses carboplatin. “We’re talking about patients where we’re running a marathon. This is a disease that’s not curable. We want to provide our patients with the best quality of life they can achieve,” she said. Although she prefers carboplatin, she said she might consider cisplatin for young patients and those with good performance status.

Based on current data, the panelists agreed that adding an anti-CTLA-4 antibody does not have a role in treating SCLC. “When I look at the tail of the curve [in CASPIAN], the tail looks better in the durvalumab-tremelimumab arm and almost catches up to the durvalumab tail. I feel like that’s because of the durvalumab and that the only thing tremelimumab is adding there is cost and a heck of a lot of toxicity,” Liu explained.

Chiang agreed that although there does not appear to be a role for anti-CTLA-4 antibodies in treating the general population of patients with extensive-stage SCLC, she is working on an investigator-initiated trial that may help tease out whether an opportunity exists for these agents to provide benefit somewhere in the treatment course for certain subpopulations with SCLC. In the trial (NCT03670056), patients with relapsed SCLC, including those previously on atezolizumab maintenance, will receive ipilimumab (Yervoy)/nivolumab (Opdivo).10 “We’re doing pretreatment and on-treatment biopsies. There’s something to be said for looking at the tumor microenvironment and specifically the infiltration of T cells, so stay tuned for that. There may be a way anti-CTLA-4 may help juice up the microenvironment so that we get T cells in there so we can have a response,” she said.

### SECOND-LINE TREATMENTS FOR SCLC

Once first-line treatment fails, patients with SCLC are left with few options. The National Comprehensive Cancer Network (NCCN) prefers that treatments for patients who relapse within 6 months include topotecan (Hycamtin) and lurbinectedin (Zepzelca), whereas rechallenge with first-line treatment is preferred for those who relapse after 6 months.11 The role of immune checkpoint inhibitors in the second-line setting remains unclear. Although single-agent nivolumab and pembrolizumab had been granted accelerated approval as treatment for patients with relapsed extensive-stage SCLC, this indication was voluntarily withdrawn by their manufacturers after these agents failed to show an OS benefit in confirmatory studies12-18 (TABLE 2).

#### Lurbinectedin

Lurbinectedin prevents transcription factors from binding to their recognition sequences, thereby inhibiting oncogenic transcription and leading to tumor cell apoptosis.14 The agent has also been shown to affect the tumor microenvironment by inhibiting activated transcription in tumor-associated macrophages.19 In June 2020, lurbinectedin received accelerated approval from the FDA for patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy, making it the first drug approved by the FDA for this indication in more than 20 years.15 Approval was based on findings from a single-arm, open-label, phase 2 basket trial (NCT02454972) that included 105 patients with recurrent SCLC.20

“An overall response by investigator assessment was seen in 37 patients, for an [overall] response rate of 35.2% [95% CI, 26.2%-45.2%],” Vivek Subbiah, MD, said. The disease control rate was 68.6% (95% CI, 58.8%-77.3%), the median duration of response was 5.3 months (range, 4.1-6.4), the median PFS was 3.5 months (95% CI, 2.6-4.3), and the median OS was 9.3 months (95% CI, 6.3-11.8).19

Lurbinectedin had a manageable safety profile, with the most common grade 3 to 4 AEs, irrespective of causality, being hematological abnormalities, particularly neutropenia (46%), leukopenia (29%), anemia (9%), and thrombocytopenia (7%).14 Serious treatment-related AEs occurred in 10% of patients, of which neutropenia and febrile neutropenia were the most common, with each affecting 5% of patients. No treatment-related deaths occurred.

Subbiah proceeded to discuss a study he presented at the European Society for Medical Oncology Virtual Congress 2020, in which investigators evaluated the activity of lurbinectedin in second-line patients with SCLC who were candidates for platinum rechallenge (ie, relapse after 6 months).21 “Interestingly, the investigator-assessed objective response rate in this cohort was 60%, with a median duration of 5.5 months and disease control rate of 95%. Of note, 60.9% and 27.1% of patients were alive at 1 and 2 years, respectively,” Subbiah said. Based on
these findings, he noted that "lurbinectin is an effective treatment for platinum-sensitive relapsed SCLC, especially in patients with a chemotherapy-free interval of greater than 180 days," potentially making this option as viable as the NCCN’s preferred approach of rechallenge in these patients.

**Putting Treatment Options Into Perspective**

In patients who are candidates for rechallenge, Liu said he considers the length of benefit of the original treatment. “If there’s a long period of benefit, I revisit the platinum-etoposide and see whether I can kick lurbinectin or topotecan as another option down the line. This is off trial, of course. We’re really pushing for trials in this subset,” he said, adding that when rechallenging with chemotherapy-immuno-therapy, he maintains the checkpoint inhibitor in select patients, despite a lack of data to support this decision.

In contrast, Iams and Chiang said they do not continue the checkpoint inhibitor. Chiang said she goes back to the platinum-etoposide for 6 months. Although she acknowledged the lurbinectin data are impressive, she is concerned that they are from a small study that did not include patients with brain metastases. “For patients whom we’ve been trying to keep out of the hospital, especially during this pandemic, I’ve been using some oral topotecan or potentially temozolomide if they have brain metastases,” she said. Taxanes are another good option for patients with brain metastases, Chiang said, adding that, anecdotally, she has seen some patients have a very good response to taxanes following checkpoint inhibitor therapy. "I don’t know whether there’s something that is boosted by adding chemotherapy post progression, as in the INSIGNIA trial [NCT03793179]. Hopefully, we’ll learn something about that," she said.

Although the FDA approvals of nivolumab and pembrolizumab were withdrawn, these agents remain options in the NCCN SCLC guidelines.11 “The NCCN small cell guidelines group ultimately voted to keep both of these drugs—although as a category 3—which indicates some discordance in the consensus,” Chiang said. She noted this discordance is not surprising because some patients have been found to do extremely well with a single-agent immune checkpoint inhibitor, even if the confirmatory trials did not show an OS benefit with these agents. Therefore, although nivolumab and pembrolizumab would now be used off label, she said they remain good options, especially for patients “who can’t tolerate chemotherapy or who have good performance status and can still be treated.”

Despite significant advances being made in SCLC, Subbiah noted that progress is approximately 15 years behind that of the non-small cell lung cancer field. “I’m sure there’s going to be a future renaissance of biomarkers and personalized therapy. Defining the subsets in SCLC represents the first step in our understanding of what drugs work best for which patient, at least preclinically. It at least gives us a guide for a path forward for personalized approaches,” he said. To help propel treatment forward, he encouraged physicians to enroll their patients with SCLC into clinical trials.

**REFERENCES**

8. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus plati-
Gynecologic Oncology Pioneer
Franco Muggia Dies at 85

**FRANCO MUGGIA, MD**, a fixture at NYU Langone's Perlmutter Cancer Center and a leader in the study and treatment of patients with gynecologic cancers, died on September 8, 2021. He was 85.

Over a career lasting more than 50 years, Muggia had a hand in the development of some of the most important drugs in chemotherapy, including bleomycin, nitrosoureas, taxanes, and his key area of interest, platinum compounds. During his time as associate director of the National Cancer Institute’s Cancer Therapy Evaluation Program, he played a crucial role in getting these agents incorporated into standard of care for clinical practice and coordinated the early clinical development of chemotherapy for patients with leukemia and lymphoma, and breast, lung, ovarian, testicular, and gastrointestinal cancers.

Throughout his career, Muggia was recognized as a worldwide thought leader in ovarian cancer therapeutics and played a leading role in the formation of the Gynecologic Oncology Group, now the GOG Foundation, Inc. He also helped found the New York Gynecologic Oncology Group and the New York Phase 1 Trials Group. In recent years, he led the Chemotherapy Foundation and helped to organize its annual meeting, the Chemotherapy Foundation Symposium, a program organized by Physicians’ Education Resource®, LLC (PER®), which draws visitors from around the world.

“Franco Muggia was a remarkable individual,” said OncologyLive® editor-in-chief Maurie Markman, MD, president of Medicine & Science at Cancer Treatment Centers of America and the 2018 Giants of Cancer Care® award winner for Gynecologic Cancer.

“He was an outstanding clinical investigator, an excellent educator, and, most important, a superb clinician. Franco participated or led some of the most important clinical studies in the gynecologic cancer arena over the past several decades. He will be greatly missed.”

Muggia was born in Torino, Italy, in 1936, but fled with his family to Quito, Ecuador, when he was 3 to escape the Benito Mussolini dictatorship. Muggia's father, described as a prominent pediatrician and drug developer, and his older brother, Albert, now a retired gastroenterologist, strongly influenced his decision to pursue a medical career.

Muggia immigrated to the United States in 1952 and later attended Yale University in New Haven, Connecticut. He then earned his MD at Weill Cornell Medical College, now Weill Cornell Medicine, in New York, New York. Muggia completed internship training at Bellevue Hospital, now NYC Health + Hospitals/ Bellevue, in New York, New York; residency at Hartford Hospital in Hartford, Connecticut; and a hematology-oncology fellowship at Columbia University in New York, New York.

After a stint as a faculty member at Albert Einstein College of Medicine in the Bronx, New York, Muggia moved to the Medicine Branch of the National Cancer Institute. There, he worked in the laboratory of oncology legends and Giants of Cancer Care® award winners Vincent DeVita Jr, MD, and George P. Canellos, MD, in a unit headed by famed clinician and investigator Paul P. Carbone, MD.

Muggia joined NYU School of Medicine in 1979 as professor of medicine and director of the Division of Medical Oncology. In 1986, he moved to the USC Norris Comprehensive Cancer Center and continued his work optimizing intraperitoneal platinum and liposomal doxorubicin therapies for patients with ovarian cancer.

He returned to NYU as director of the former Kaplan Cancer Center at NYU Medical Center from 1996 to 1997 before serving as director of the Division of Medical Oncology at NYU Langone Health’s Perlmutter Cancer Center until 2009. After stepping down as division chief, he served as a senior faculty member and continued his commitment to clinical care, research, and educating the next generation of physician-scientists.

Muggia is survived by his wife, Anna; their daughters, Diana, Vickie, Paola, and Julia; 10 grandchildren, and his older brother, Albert.
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