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by ONCLIVE® STAFF

Throughout the past year, investigators have presented findings from clinical trials that have ushered in a new era of care for patients across tumor types. The introduction and approval of novel agents and combinations have altered sequencing standards and introduced new clinical questions to answer in the coming years.

DEPARTMENTS

From the Editor
It Is Time to Reexamine Control Arms in Phase 3 Trials
By Maurie Markman, MD

Medical World News®
40 FDA Digest
41 Drug Spotlight: Pembrolizumab (Keytruda)
36 Abemaciclib (Verzenio)

ONCOLOGY & BIOTECH NEWS®
39TH ANNUAL CFS®
40 Checkpoint Blockade Moves Needle in Molecularly Driven Endometrial Cancer Paradigm
44 Bispecific Monoclonal Antibodies Lead Immune-Driven Therapies Into the Future
51 Treatment Options Continue to Increase in Low-Risk MDS

Clinical Trial in Focus
54 Novel Combination Looks to Capitalize on Synergy of B7-H3/PD-1 Blockade

Clinical Perspectives
61 Influx of Therapies in NETs Prompts Questions Over Combinations and Sequencing
63 Saif Shares Insights on Single-Agent PARP Inhibitors and Combination Therapies for Pancreatic Cancer

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LONG-AWAITED DATA FROM TRIALS have introduced new standards of care, resulted in the approval of novel agents, and challenged investigators to view new strategies including sequencing of adjuvant therapies, radiopharmaceuticals, among others. With the highlights from meetings set for publication, investigators are setting their sights on how these findings will factor into clinical practice and what new questions await them in the new year and beyond.

Data from confirmatory trials for agents granted accelerated approval will either solidify their role in the treatment landscape or bring back the standards of care that were challenged. Additionally, efforts may be initiated to move other drugs that have proven effective in later lines of therapy forward in sequencing in an effort to provide benefit to patients earlier in the course of their disease.

Approvals of agents under development for years do not mark the end of the discovery cycle but prompt the beginning or encourage the continuation of another. For example, the buzz generated around fam-trastuzumab deruxtecan-nxki (Enhertu) at the 2019 San Antonio Breast Cancer Symposium led not only to the FDA approval of the agent shortly thereafter¹ for patients with metastatic HER2-positive breast cancer, but also propelled efforts to further define the role of agent in the treatment landscape. Specifically, data presented from the first head-to-head trial of trastuzumab deruxtecan vs standard of care ado-trastuzumab emtansine (T-DM1; Kadcyla).² Data from the DESTINY-Breast03 trial (NCT03529110) favored the antibody-drug conjugate over T-DM1, but investigators were presented with more questions surrounding the use of the agent over other anti-HER2 therapies and at different points in disease course.

As these clinical questions begin to come to light, so do questions of adaptability in the trial design space. In this issue’s column, OncologyLive®’s editor in chief Maurie Markman, MD, tackles the topic with a discussion on appropriate comparator arms for phase 3 trials. “There is no easy answer to the question being posed in this commentary and there is no intent here to criticize any drug manufacturer or the FDA for efforts to find new drugs with clinically meaningful activity in ovarian cancer. However, it is critical to emphasize the compromises that are likely required in the regulatory process to permit efficient drug development. But we must keep in mind the potential for subsequent, and almost certain, confusion among clinicians who will be required to interpret clinical trial data without the benefit of a direct comparison to what has become a rapidly changing standard of care on behalf of their patients.

Looking ahead to 2022, OncLive® will continue to provide in-depth analysis of the latest data with insights from key opinion leaders in the field. The OncLive Peer Exchange®, Rapid Readouts, and Talk programs will invite experts to contextualize and challenge findings presented at major conferences and meetings. In addition, programs sponsored by Physicians’ Education Resource®, LLC (PER®) will bring together members of the community to unpack how the latest research can be best integrated in the clinical setting.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
ARE YOU THINKING DEEP ENOUGH IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too\(^1\)\(^2\)

With each relapse, multiple myeloma becomes increasingly difficult to control. As the disease progresses, very few patients (less than 5%) experience a deep response.\(^1\)\(^2\) However, evidence suggests a deep response may be associated with improved PFS and OS.\(^1\)\(^3\) Therefore, shouldn’t a goal of treatment be to achieve a deep response in as many patients as possible?

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OS=overall survival; PFS=progression-free survival

It Is Time to Reexamine Control Arms in Phase 3 Trials

by MAURIE MARKMAN, MD

As the cancer arena continues to rapidly evolve, few if any would question that there are multiple potentially problematic issues confronting the oncology research community and drug regulatory agencies. These include strategies to appropriately evaluate small but clinically relevant patient subsets for whom traditional phase 3 randomized clinical trials are difficult, if not impossible, to complete in a realistically timely manner, and decisions related to the requirements for biosimilar drugs to achieve approval for the multiple indications originally achieved by the original brand name pharmaceutical agent.

One increasingly problematic area that, in the opinion of this commentator, has received inadequate discussion in the oncology literature is the question of the appropriate control arms in studies of agents designed to achieve approval by the FDA and other drug regulatory agencies for commercial sale.

It would not be difficult to find examples of controversy in this area in other tumor types, but agents for the treatment of ovarian cancer will be the focus here both because of the research interests of this commentator and valid concerns regarding the question in this malignancy.

CONTROL ARMS COME INTO FOCUS

The platinum agents cisplatin and carboplatin have played a foundational role for more than 40 years as the primary chemotherapeutic treatments for patients with epithelial ovarian cancer. Over a period of years, investigators examined cisplatin chemotherapy in combination with cyclophosphamide, doxorubicin, or both, before ultimately settling on cisplatin and cyclophosphamide as being equally effective but overall less toxic than other approaches. Subsequently, data from randomized phase 3 trials revealed that the substitution of carboplatin for cisplatin resulted in equivalent survival with a more favorable adverse effect profile. In a landmark study reported 25 years ago, the use of paclitaxel in place of the alkylating agent was revealed to improve survival in advanced disease. Finally, to validate the scientific question, results of a randomized phase 3 trial confirmed that the delivery of carboplatin rather than cisplatin produced the same statistically defined overall survival outcome but with a more tolerable toxicity profile.

The intent of this brief historical summation is to emphasize the rational progression of evidence-based randomized trials in this era conducted over a period of several decades. The superior treatment arm, evaluated for efficacy, toxicity, or both, served as the uncontested control arm in the next series of industry- or cooperative group–based clinical trials. During this time multiple approaches were examined, each compared with a control arm of the systemic administration of a platinum agent and paclitaxel. For example, investigators evaluated the addition of a third cytotoxic drug, the substitution of another cytotoxic agent for paclitaxel, and the delivery of more cycles or higher doses of platinum therapy. Results demonstrated that only the regional delivery of platinum and possibly paclitaxel produced a superior outcome in progression-free survival (PFS) or overall survival.

Based on considerable clinical experience within the oncology community, the extent and duration of a prior response to platinum-based therapy is now used by the FDA and other national drug regulatory agencies as a simple paradigm for examining and potentially approving novel drugs and treatment strategies in the second- or later-line settings (eg, in platinum-sensitive recurrent ovarian cancer or platinum-resistant ovarian cancer).

Fortunately for patients with ovarian cancer, there has been a striking change in the development of effective antineoplastic strategies for the malignancy over the past decade. Specifically, this includes the use of the antiangiogenic agent bevacizumab (Avastin) and several PARP inhibitors, which have significantly improved clinical outcomes and radically altered the existing standard of care. Further, an impressive number of novel antineoplastic agents are in early- or later-stage development for the treatment of this cancer.

Now we come to the problem that may soon become a critical item for discussion among regulatory agencies and oncologists treating ovarian cancer, assuming the approval of 1 or more of these novel drugs in the not-so-distant future:

What was the control arm of the randomized phase 3 trial leading to approval and, most critically, do the
existing evidence-based trial data demonstrating the utility of a novel strategy actually indicate superiority (or equivalence) to the current standard of care in a specific clinical setting?

Consider, for example, the setting of platinum-resistant ovarian cancer, in which data from the paradigm-changing AURELIA study (NCT00976911) showed that the combination of bevacizumab plus 1 of 3 cytotoxic agents (weekly paclitaxel, pegylated liposomal doxorubicin, or weekly or every-3-week topotecan) with known but modest clinical activity in this setting impressively improved PFS vs one of the cytotoxic agents alone. The median PFS was 6.7 vs 3.4 months, respectively (HR, 0.48; 95% CI, 0.38-0.60; \( P < .001 \)). These data led to the approval of bevacizumab in combination with standard chemotherapy for patients with platinum-resistant, recurrent ovarian cancer.\(^6\)

Suppose a subsequently conducted phase 3 trial did not include the delivery of 1 of these 3 cytotoxic drugs plus bevacizumab and instead used single-agent cytotoxic chemotherapy as the study control arm. If the investigative arm were statistically significantly superior, would it be legitimate to scientifically conclude that this regimen can be substituted for the established 2-drug chemotherapeutic combination in routine management? Further, would this be a clinically acceptable evidence-based conclusion even if it was given the OK by the FDA?

There is no easy answer to the question being posed in this commentary and there is no intent here to criticize any drug manufacturer or the FDA for efforts to find new drugs with clinically meaningful activity in ovarian cancer. However, it is critical to emphasize the compromises that are likely required in the regulatory process to permit efficient drug development. But we must keep in mind the potential for subsequent, and almost certain, confusion among clinicians who will be required to interpret clinical trial data without the benefit of a direct comparison to what has become a rapidly changing standard of care on behalf of their patients. ■

REFERENCES

Melphalan Flufenamide Myeloma Indication Is Removed in US

Oncopeptides AB has decided to withdraw from the US market the indication of melphalan flufenamide (Pepaxto) in combination with dexamethasone for the treatment of select adult patients with relapsed or refractory multiple myeloma.

In February, the FDA granted accelerated approval for the combination for patients in this population who have received at least 4 prior lines of therapy with disease that is refractory to at least 1 proteasome inhibitor, 1 immunotherapy agent, and 1 CD38-directed monoclonal antibody.

The decision was based on findings from the phase 2 HORIZON trial (NCT02963493), which demonstrated that the doublet elicited an overall response rate of 23.7% (95% CI, 15.7%-33.4%) in the efficacy population (n = 97). Among responders, 14.4% achieved partial response and 9.3% had a very good partial response. The median duration of response was 4.2 months (95% CI, 3.2-7.6).

Results from the confirmatory phase 3 OCEAN trial (NCT03151811), which compared melphalan flufenamide and dexamethasone (n = 246) with pomalidomide (Pomalyst) and dexamethasone (n = 249) in patients with relapsed or refractory disease, showed an HR for overall survival in the intention-to-treat population of 1.104. The FDA noted that it did not consider these data to meet the criteria of a confirmatory trial.

FDA Pushes Back Decision Date for Cilta-Cell BLA in Relapsed/Refractory Myeloma

The FDA has extended the Prescription Drug User Fee Act target date for the biologics license application (BLA) seeking the approval of ciltacabtagene autoleucel (cilta-cel) for use in adult patients with relapsed or refractory multiple myeloma. The new decision date for the application is February 28, 2022.

On October 28, Janssen Pharmaceutical Companies of Johnson & Johnson was alerted to the extension to allow adequate time to review recently submitted data associated with an updated analytical method following an information request issued by the regulatory agency. No additional data were requested of Legend Biotech and Janssen Biotech Inc, the developers of cilta-cel.

The BLA for cilta-cel is supported by data from the phase 1b/2 CARTITUDE-1 trial (NCT03548207), which showed that when the product was administered at the recommended phase 2 dose (0.75 × 10^6 chimeric antigen receptor–positive viable T cells per kg), it resulted in an overall response rate of 97% (95% CI, 91.2%-99.4%) among 97 patients. The stringent complete response rate was 67%, and the median time to first response was 1 month (interquartile range, 0.9-1).

FDA has granted accelerated approval for use in adult patients with relapsed or refractory myeloma. The new decision date is February 28, 2022.
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Drug Spotlight | PEMBROLIZUMAB (KEYTRUDA)

Pembrolizumab Combination Advances Standard of Care in TNBC
by KYLE DOHERTY

PEMBROLIZUMAB (KEYTRUDA) HAS ADDED another indication to its already long list of clinical uses. On July 26, 2021, the FDA approved the PD-1 inhibitor for patients with high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.¹

The approval was based on findings from the phase 3 KEYNOTE-522 trial (NCT03036488), which showed that patients treated with pembrolizumab plus chemotherapy (n = 784) experienced a pathological complete response (pCR) rate of 63% (95% CI, 59.5%-66.4%) compared with 55.6% (95% CI, 50.6%-60.6%) in patients receiving placebo plus chemotherapy (n = 390).² In an interview with OncologyLive®, Peter Schmid, MD, PhD, a professor of medicine at Cancer Research UK Barts Centre in London, England, discussed how this approval defines a new standard of care for patients with TNBC.

What were the key takeaways from the KEYNOTE-522 data?

[We already knew that] immune therapy could provide a benefit in TNBC. There was single-agent activity [with pembrolizumab] in metastatic TNBC trials, and results of randomized phase 2 trials showed a substantial benefit from adding immunotherapy to chemotherapy. It was clear from the metastatic studies that single-agent immunotherapy would not be the optimal strategy forward. [However, there was] a clear synergistic signal and a rationale to combine chemotherapy with immunotherapy because chemotherapy can upregulate CD8-positive cells and PD-L1. [Chemotherapy] can also downregulate some of the inhibitory or regulatory T cells and, most importantly, it can lead to antigen release, which enables immunotherapy to work better. When we were designing [treatment strategies for] early breast cancer we were aware there was a clinical need to improve outcomes for patients with stage II and stage III TNBC. Neoadjuvant chemotherapy is the standard of care; therefore, it was a logical next step to combine neoadjuvant chemotherapy with pembrolizumab.

We saw a substantial, and meaningful increase in the rate of pCR with pembrolizumab compared with chemotherapy alone. In addition, according to the results of the primary analysis, after a median follow-up of 39 months, we saw that the addition of pembrolizumab significantly improved event-free survival (EFS). The EFS rate was 84.5% with pembrolizumab vs 76.8% with [placebo]—that’s a substantial, important difference.

Another important observation is that the benefit of immunotherapy when looking at EFS seems to be consistent through all subgroups. That includes patients with node-positive or node-negative disease. Patients with stage II or stage III disease have the same relative benefit with the addition of pembrolizumab. Interestingly, patients with PD-L1-positive tumors have the same relative benefit as patients with PD-L1-negative tumors. These data are in clear contrast to what we saw in the metastatic setting, probably because of the higher plasticity of those tumors.

Additionally, a preplanned analysis examined EFS by pCR rate, looking at whether patients with immunotherapy do better than patients [who did not receive] immunotherapy. The patients who achieved pCR with the addition of pembrolizumab have a slightly better outlook with an EFS rate of 94.4% after 3 years compared with 92.5% [for those without pembrolizumab treatment]; the HR was approximately 0.7. Most importantly, if you look at the patients who had residual disease at the time of surgery, where one would be tempted to say the treatment didn’t work optimally, we saw a substantial benefit from immunotherapy. The 3-year EFS rate for patients with residual disease was 67.4% if they received immunotherapy and 56.8% for patients who received chemotherapy and placebo.

Looking at tolerability, most adverse effects [AEs] were consistent with what we know from checkpoint inhibitors given alone or in combination with chemotherapy. Most of the events observed during the study were chemotherapy-related, but there were also immune-mediated AEs consistent with the known profile. The most common AEs were endocrine changes and skin reactions [and] were mostly observed in the neoadjuvant phase. In the 6 months after surgery, when patients received pembrolizumab alone, there was a very low incidence of these AEs.

How does this approval potentially shift the treatment paradigm of TNBC?

For me, the KEYNOTE-522 data define a new standard of care for patients with stage II-III TNBC. This is a high-risk disease. We have been able to demonstrate that we didn’t just increase response rates but also can now improve long-term outcomes, reducing recurrences by nearly 40%. This is a massive step forward and should be a new standard of care, provided access is possible.

What does the future hold for this therapy in this patient population?

This trial has clearly established that immunotherapies should be part of therapy for patients with stage II-III disease. We don’t yet know what the role of immunotherapy may be [for patients with] stage I disease and trials are certainly warranted in this setting, especially as an option to de-escalate some of the chemotherapy if immunotherapy was added [to treatment for] patients with low-risk disease.

The second question we can’t address for now [with the] KEYNOTE-522 data is to what degree patients benefit from the 6-month adjuvant phase of the therapy. Now, we can only say 1 year of immunotherapy delivers benefit. How much of this [is attributable] to the first 6 months vs the second 6 months we don’t know. For patients who have achieved pCR, it’s certainly a consideration to see [whether] they may have a similar benefit if they only receive immunotherapy in the early setting.

A third question [regards] the chemotherapy strategy. [In KEYNOTE-522] we selected the most effective chemotherapy strategy, which has now been confirmed. [However], it is worthwhile to explore whether all patients will require this chemotherapy strategy and whether similar outcomes could be achieved with other chemotherapy strategies.

REFERENCES
FDA grants approval to pembrolizumab (Keytruda) for the treatment of patients with high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

**Mechanism of action:**
- Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

**How supplied:**
- 100 mg/4 mL (25 mg/mL) solution in a single-dose vial

**Dose:**
- 200 mg every 3 weeks or 400 mg every 6 weeks

**Company:** Merck

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**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
</tr>
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<tbody>
<tr>
<td>Pembrolizumab plus chemotherapy (n = 784)</td>
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<tr>
<td>Placebo plus chemotherapy (n = 390)</td>
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**ECOG performance status of 1 (%)**

<table>
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<th>Pembrolizumab</th>
<th>Placebo</th>
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<tr>
<td>86.5%</td>
<td>87.4%</td>
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<td>13.5%</td>
<td>12.6%</td>
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**PD-L1 positive†**

<table>
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<th>Pembrolizumab</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>83.7%</td>
<td>81.3%</td>
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**OF PATIENTS HAD**

- A CPS ≥ 1

**Nodal involvement**

<table>
<thead>
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<th>Pembrolizumab</th>
<th>Placebo</th>
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<td>51.7%</td>
<td>51.3%</td>
</tr>
<tr>
<td>48.3%</td>
<td>48.7%</td>
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</tbody>
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**REFERENCES**

UKONIQ is indicated for the treatment of adult patients with:

- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen
- Relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy

**IMPORTANT SAFETY INFORMATION**

**Infections:** Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

**Neutropenia:** Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 10^9/L (Grade 3–4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia.

**Diarrhea or Non-Infectious Colitis:** Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., >6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with anti-diarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis.

**Hepatotoxicity:** Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

**Severe Cutaneous Reactions:** Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening
UKONIQ is indicated for the treatment of adult patients with:

IMPORTANT SAFETY INFORMATION

weekly in patients with neutrophil count <1 x 10^9

at least every 2 weeks for the first 2 months of UKONIQ and at least

Grade 4 neutropenia developed in 9%. Monitor neutrophil counts

UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and

monitor patients for CMV reactivation by PCR or antigen test at

or viremia, withhold UKONIQ until infection or viremia resolves. If

Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ

Grade 3 or 4 infection, withhold UKONIQ until infection has resolved.

Monitor for any new or worsening signs and symptoms of infection,

with UKONIQ to prevent CMV infection, including CMV reactivation.

Pneumocystis jirovecii

frequent Grade ≥3 infections included pneumonia, sepsis, and

of 335 patients, with fatal infections occurring in <1%. The most

serious, including fatal, infections occurred in patients

treated with UKONIQ. Grade 3 or higher infections occurred in 10%

in 221 patients who received

least one month after the last dose.

fetus. Advise females and males with female partners of reproductive

pregnancy. Advise pregnant women of the potential risk to a

Based on findings in animals and its mechanism

potentially contributing medications. Withhold

UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume

UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue

UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or

DRESS of any grade. Provide supportive care as appropriate.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5: UKONIQ

contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible

persons, frequently in patients who also have aspirin hypersensitivity.

Embryo-fetal Toxicity: Based on findings in animals and its mechanism

action, UKONIQ can cause fetal harm when administered to a

pregnant woman. Advise pregnant women of the potential risk to a

fetus. Advise females and males with female partners of reproductive

potential to use effective contraception during treatment and for at

least one month after the last dose.

Serious adverse reactions occurred in 18% of 221 patients who received

UKONIQ. Serious adverse reactions that occurred in ≥2% of patients

were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary

tract infection (2%). Permanent discontinuation of UKONIQ due to

an adverse reaction occurred in 14% of patients. Dose reductions

of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction

occurred in 43% of patients. The most common adverse reactions (>15%), including laboratory abnormalities, in 221 patients who received UKONIQ were increased
creatinine (79%), diarrhea-colitis (58%, 2%), fatigue (41%), nausea
(38%), neutropenia (33%), ALT increase (33%), AST increase (32%),
musculoskeletal pain (27%), anemia (27%), thrombocytopenia (26%),
upper respiratory tract infection (21%), vomiting (21%), abdominal
pain (19%), decreased appetite (19%), and rash (18%).

Lactation: Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed
during treatment with UKONIQ and for at least one month after the

last dose.

Please see Brief Summary of full Prescribing Information on the

following pages.


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06/2021 US-UMB-2000079

VISIT UKONIQ.COM TO LEARN MORE.
UKONIQ® (umbralisib) tablets, for oral use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

1.1. Marginal Zone Lymphoma
UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. This indication is approved under accelerated approval based on overall response rate (see Clinical Studies [14.1]). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2. Follicular Lymphoma
UKONIQ is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy. This indication is approved under accelerated approval based on overall response rate (see Clinical Studies [14.2]). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2. CONTRAINDICATIONS
None.

5. WARNINGS AND PRECAUTIONS
5.1. Infections
Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. The median time to onset of Grade ≥3 infection was 2.4 months (range: 1 day to 21 months) (see Adverse Reactions [6.1]).

Monitor neutrophil counts at least every 2 weeks for the first [see Adverse Reactions (6.1)].

Grades 3 and 4 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 3% of 335 patients. Withhold UKONIQ until infection or viremia resolves. If UKONIQ is withheld for CMV infection, including CMV reactivation [see Dosage and Administration (2.3)]. Provide prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation [see Dosage and Administration (2.3)].

5.2. Neutropenia
Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9% [see Adverse Reactions (6.1)]. The median time to onset of Grade 3 or 4 neutropenia was 45 days. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil counts <1 x 10^9/L (Grade 3). Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia [see Dosage and Administration (2.3)].

5.3. Diarrhea or Non-infectious Colitis
Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9% [see Adverse Reactions (6.1)]. The median time to onset for any grade diarrhea or colitis was 1 month (range: 1 day to 23 months), with 75% of cases occurring by 2.9 months.

Withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly [see Dosage and Administration (2.3)].

5.4. Hepatotoxicity
Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in ≥4% of patients included diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Fatal adverse reactions occurred in <1% of patients who received UKONIQ, including exfoliative dermatitis. Permanently discontinue UKONIQ in an adverse reaction occurred in 14% of patients. Adverse reactions which resulted in permanent discontinuation of UKONIQ occurred in ≥5% of patients included diarrhea-colitis (4%) and transaminase elevation (5%).

Dose reductions of UKONIQ due to an adverse reaction occurred in 43% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included diarrhea-colitis (3%), transaminase elevation (7%), neutropenia (5%), vomiting (5%), and upper respiratory tract infection (5%).

The most common (>15%) adverse reactions, including laboratory abnormalities, were increased creatinine, diarrhea-colitis, fatigue, infection, liver function test abnormalities, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite, and rash.

Table 3 describes the adverse reactions in the pooled safety population of 221 patients with marginal zone lymphoma and follicular lymphoma who received the recommended dosage.

Table 3: Adverse Reactions Reported (≥10%) in Patients With Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Any Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil decreased</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

*Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading system.
8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy Risk Summary

Based on findings from animal studies and the mechanism of action (see Clinical Pharmacology [12.1]) UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of umbalisib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and structural abnormalities at maternal exposures (AUC) comparable to those in patients at the recommended dose of 800 mg (see Data). Advise pregnant women to avoid breastfeeding.

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

8.2. Lactation Risk Summary

There are no data on the presence of umbalisib in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions from umbalisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose.

8.3. Females and Males of Reproductive Potential

UKONIQ may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations [8.1]).

8.3.1. Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating UKONIQ.

8.3.2. Contraception

Females

Advise female patients of reproductive potential to use highly effective contraception during treatment with UKONIQ and for one month after the last dose.

Males

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

8.3.3. Infertility

Males

Based on the findings from mice and dogs, UKONIQ may impair male fertility (see Nonclinical Toxicology [13.1]). Trend for reversibility was noted in dogs 30 days after the last dose.

8.4. Pediatric Use

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

8.5. Geriatric Use

Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, 56% of patients were 65 years of age or older, while 19% were 75 years of age and older. No overall differences in effectiveness or pharmacokinetics were observed between these patients and younger patients. In patients 65 years of age and older, 23% experienced serious adverse reactions compared to 12% of patients younger than 65 years of age. There was a higher incidence of infectious serious adverse reactions in patients 65 years of age or older (13%) compared to patients younger than 65 years of age (4%).

8.6. Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance [Clcr] 30 to 89 mL/min estimated by Cockcroft-Gault equation) (see Clinical Pharmacology [12.3]). UKONIQ has not been studied in patients with severe renal impairment (Clcr < 30 mL/min).

8.7. Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin < upper limit of normal [ULN]) and AST > ULN or total bilirubin > 1.5 × ULN and any KST (see Clinical Pharmacology [12.3]). UKONIQ has not been studied in patients with moderate (total bilirubin > 1.5 to 3 × ULN and any KST) or severe hepatic impairment (total bilirubin > 3 × ULN and any KST).

14. CLINICAL STUDIES

14.1. Marginal Zone Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTXG-025 (NCT02793583), an open-label, multi-center, multi-cohort trial. Patients with MZL were required to have received at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor.

Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity. A total of 69 patients with MZL (extranodal (N=38), nodal (N=20), and splenic (N=11)) were enrolled in this cohort. The median age was 67 years (range: 24 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, 7% were Other, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy.

Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.3 months (range: 15.0 to 28.7 months). Efficacy results are shown in Table 5.

Table 5: Efficacy Results in Patients with MZL (Study 205)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=69)</th>
<th>95% CI</th>
<th>95% CI</th>
<th>Range, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRR</td>
<td>34 (49)</td>
<td>37.0, 61.6</td>
<td>11 (16)</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>CR</td>
<td>23 (33)</td>
<td>16 (27)</td>
<td>16 (27)</td>
<td>Range, months</td>
</tr>
<tr>
<td>PR</td>
<td>23 (33)</td>
<td>16 (27)</td>
<td>16 (27)</td>
<td>Median, months (95% CI)</td>
</tr>
</tbody>
</table>

Cl, confidence interval; CR, complete response; DRR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; NE, not evaluable; NR, not reached; PR, partial response.

*Per IRC according to Revised International Working Group Criteria

†Based on Kaplan-Meier estimation

Table 6: Efficacy Results in Patients With Relapsed or Refractory FL (Study 205)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=117)</th>
<th>95% CI</th>
<th>95% CI</th>
<th>Range, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRR</td>
<td>50 (43)</td>
<td>33.6, 52.2</td>
<td>4 (3.4)</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>CR</td>
<td>23 (33)</td>
<td>16 (27)</td>
<td>16 (27)</td>
<td>Range, months</td>
</tr>
<tr>
<td>PR</td>
<td>23 (33)</td>
<td>16 (27)</td>
<td>16 (27)</td>
<td>Median, months (95% CI)</td>
</tr>
</tbody>
</table>

Cl, confidence interval; CR, complete response; DRR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; PR, partial response.

*Per IRC according to Revised International Working Group Criteria

†Based on Kaplan-Meier estimation

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The median time to response was 4.4 months (range: 2.2 to 15.5 months).

17. PATIENT COUNSELING INFORMATION

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

Infections

Advise patients that UKONIQ can cause serious infections that may be fatal. Advise patients to immediately report any signs or symptoms of infection (e.g., fever, chills, weakness) (see Warnings and Precautions [5.1]).

Neutropenia

Advise patients of the need for periodic monitoring of blood counts and to notify their healthcare provider immediately if they develop a fever or any signs of infection (see Warnings and Precautions [5.2]).

Diabetes or Non-Infectious Colitis

Advise patients that they may experience loose stools or diarrhea and should contact their healthcare provider with any persistent or worsening diarrhea. Advise patients to maintain adequate hydration (see Warnings and Precautions [5.3]).

Advisers of the possibility of colitis and to notify their healthcare provider of any abdominal pain/distress (see Warnings and Precautions [5.3]).

Severe Cutaneous Reactions

Advise patients that UKONIQ may cause a severe skin rash and to notify their healthcare provider immediately if they develop a new or worsening skin rash (see Warnings and Precautions [5.4]).

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential 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 [5.7]). Advise males of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose (see Use in Specific Populations [8.1, 8.3]).

Advisers of females of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose (see Use in Specific Populations [8.3]).

Lactation

Advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose (see Use in Specific Populations [8.3]).

Infertility

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

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5 Advise patients that UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain susceptible persons (see Warnings and Precautions [5.6]).

Administration

Inform patients to take UKONIQ orally once daily at approximately the same time each day with food and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to crush, break, cut or chew tablets (see Dosage and Administration [2.1]).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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UKONIQ®  umbalisib  200 mg tablets
Abemaciclib Becomes First Agent of its Kind Approved for Adjuvant Treatment of Early Breast Cancer

by KYLE DOHERTY

ABEMACICLIB, A CDK4/6 INHIBITOR, has been approved in combination with tamoxifen or an aromatase inhibitor for the adjuvant treatment of adult patients with hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence and a Ki-67 score of at least 20%, as determined by an FDA-approved test, based on data from the phase 3 MonarchE trial (NCT03155997).

The 36-month invasive disease-free survival rate among patients treated with abemaciclib plus tamoxifen or an aromatase inhibitor (n = 1017) was 86.1% (95% CI, 82.8%-88.8%) compared with 79% (95% CI, 75.3%-82.3%) in patients treated with tamoxifen or an aromatase inhibitor alone (n = 986). Approximately 16% of patients in the control group experienced an event vs 10.2% in the experimental arm (HR 0.0626; 95% CI, 0.488-0.803; P = .0042).

In an interview with OncologyLive®, Stephen Johnston, MD, PhD, head of Medical Oncology and head of the Breast Unit at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research in London, England, provided insight on the effect the approval of the CDK4/6 inhibitor has for patients with early breast cancer and how it will advance investigative efforts in this space.

What was the clinical rationale for studying this combination in this patient population?

In the MonarchE trial, we looked at patients who were deemed to be at high risk of recurrence following a diagnosis of [hormone receptor-] positive, HER2-negative early breast cancer. We were specifically selecting those who had lymph node–positive disease. We know they’re at higher risk. The layers of risk on top of that [baseline] were addressed as [either] 4 or more [positive] nodes, or if they had 1 to 3 [positive] lymph nodes. [Also,] patients had additional risks, such as a large tumor, high grade, or high proliferation. Despite the best standard of care, we estimated this population would, on average, [experience] relapse at a rate from 20% to 30% in the first 3 to 5 years, so there was room for improvement.

CDK inhibitors have already been shown to add [benefit] to endocrine therapy in advanced disease, as they overcome endocrine resistance and they control the cancer for longer. The question was: In early breast cancer, could we select an at-risk population and show that adding [a CDK inhibitor] for 2 years in addition to their endocrine therapy would [reduce the rate of] early recurrences in the first 2 to 3 years?

What does the future hold for abemaciclib in combination with endocrine therapy?

There are approximately 6 or 7 ongoing studies with CDK inhibitors in the early breast cancer setting, looking to see if we can further refine the group of patients who benefit. Trials in both a neoadjuvant and adjuvant setting are [evaluating CDK inhibitors] head-to-head against chemotherapy because chemotherapy is not always the answer for luminal hormone positive–breast cancer. That will be important because you could spare the toxicity of chemotherapy with this effective combination if it can be proven to be as effective or better.

Other studies are to refine the selection of endocrine-resistant disease. [Investigators are using a] technique of very short-term exposure to a hormone treatment in the 2 or 3 weeks before surgery and measuring Ki-67 [expression] to see whether hormone treatment switches that off. If it does, hormone treatment alone can be very good. However, hormone treatment will not switch off cell proliferation in approximately 20% of patients. [To overcome this,] investigators of the POETIC-A study [NCT04584853] will identify those where the proliferation is not being switched off and randomize them to abemaciclib [or endocrine therapy] after [surgery].

The label [indicates abemaciclib] for large, node-positive tumors. The [patients in POETIC-A] may have smaller tumors or node-negative disease, [representative of] a group of patients with biologically resistant tumors to endocrine therapy, who may not have high clinical pathological risk factors. That may be the next setting where this drug could be refined to have a niche role.

REFERENCE

PIVOTAL CLINICAL TRIAL

MonarchE (NCT03155997) was a phase 3 open-label, 2-cohort multicenter trial that randomized adult patients with hormone receptor-positive, HER2-negative, node-positive, resected, early breast cancer with clinical and pathological features consistent with a high risk of disease recurrence to receive 2 years of abemaciclib plus physician’s choice of standard endocrine therapy or standard endocrine therapy alone. Patients enrolled to cohort 1 had high Ki-67 expression (≥ 20%).

BASELINE PATIENT CHARACTERISTICS

Median age, years (range) 51 (24-88) N = 2003

Prior treatment

Radiotherapy 37%
Adjuvant chemotherapy 60%
Neoadjuvant chemotherapy 95%

Initial endocrine therapy

Letrozole 39%
Tamoxifen 33%
Anastrozole 19%
Exemestane 8%

Efficacy results in cohort 1 of the MonarchE trial

Outcome | Abemaciclib plus tamoxifen or an aromatase inhibitor (n = 1017) | Tamoxifen or an aromatase inhibitor (n = 986)
--- | --- | ---
36-month iDFS rate (95% CI) | 86.1% (82.8%-88.8%) | 79.0% (75.3%-82.3%)
Number of patients with an event | 10.2% | 16.0%

HR, 0.626; 95% CI, 0.488-0.803; P = .0042

iDFS, invasive disease-free survival.

Warnings and Precautions

- Diarrhea
- Neutropenia
- Interstitial lung disease or pneumonitis
- Hepatotoxicity
- Venous thromboembolism
- Embryo-fetal toxicity

Commonly reported adverse effects in the MonarchE trial

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Abemaciclib plus tamoxifen or an aromatase inhibitor (n = 2791)</th>
<th>Tamoxifen or an aromatase inhibitor (n = 2800)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>84%</td>
<td>8%</td>
</tr>
<tr>
<td>Infections</td>
<td>51%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Rash</td>
<td>11%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Intention-to-treat population.
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 status1-4.

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.
YOU RESPOND WITH ZEJULA

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS

- **OVERALL POPULATION**
  - Reduction in the risk of progression or death
  - MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR, 0.62; 95% CI, 0.50-0.76) P<0.0001

- **HRd POPULATION**
  - Reduction in the risk of progression or death
  - MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO (HR, 0.43; 95% CI, 0.31-0.59) P<0.0001

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

Important Safety Information (continued)

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

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

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

Please see Brief Summary on the following pages.


IL = 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.
5.3 Hypertension and Cardiovascular Effects

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

In 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 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days).

Discontinuation due to hypertension occurred in <1% of patients.

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].

6.4 Posterior Reversible Encephalopathy Syndrome

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 [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 Clinical Pharmacology (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.

Approse 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 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 of FD&C 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 (5.2))
• Hypertension and cardiovascular effects (see Warnings and Precautions (5.3))
• Posterior reversible encephalopathy syndrome (see Warnings and Precautions (5.4))

6.1 Clinical Trials Experience

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

The most common adverse reactions of all grades in >10% of 3,134 patients who received ZEJULA in the pooled PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (50%), constipation (35%), musculoskeletal pain (35%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (10%), dizziness (14%), acute kidney injury (13%), urinary tract infection (6%), and hyperglycemia (11%).
toxicity caused by previous chemotherapy (≤Grade 1). Monitor patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, neutropenia, and/or pancytopenia occurred in 4%, 2%, and 1%, respectively, of patients treated with ZEJULA. In patients who were administered ZEJULA, myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) occurred in 0.3% of patients treated with ZEJULA in clinical trials. The most common terminologies for adverse events are given in Table 7.

Myelodysplastic Syndrome/Acute Myeloid Leukemia

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

The safety of ZEJULA for the treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been previously treated with chemotherapy and who have progressed more than 12 weeks after their last chemotherapy cycle is described in Table 2. The safety of ZEJULA monotherapy for the maintenance treatment of adult patients with high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have HRD positive status defined by either: a deleterious or suspected deleterious BRCA1 or BRCA2 variant, or a known germline BRCA1 or BRCA2 mutation, is described in Table 3. The safety of monotherapy with ZEJULA 300 mg once daily has been studied in PRIMA, a randomized double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11 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 anaemia (8%) 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 anaemia (3% each) and nausea (2.4%). Adverse reactions related to dose reduction or interruption in >2% of patients, most frequently from thrombocytopenia (40%), anaemia (23%), and neutropenia (15%). Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%), anaemia (20%), and neutropenia (18%). The median exposure to ZEJULA in these patients was 250 days. Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

The following adverse reactions and laboratory abnormalities have been identified in >1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, and epistaxis. The safety of ZEJULA 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the included QUADRA population, the median duration was 4 months (range: 0.1 to 30 months). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest. Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%). Permanent discontinuation due to adverse reactions occurred in 21% of patients who received ZEJULA. Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anaemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%). Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.
**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:** Neutropenia

**Immune System Disorders:** Hypersensitivity (including anaphylaxis)

**Nervous System Disorders:** Posterior reversible encephalopathy syndrome (PRES)

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

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

**Skin and Subcutaneous Tissue Disorders:** Photosensitivity.

**Vascular Disorders:** Hypertensive crisis.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

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

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

**8.2 Lactation**

**Risk Summary**

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

**8.3 Females and Males of Reproductive Potential**

**Zejula can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].**

**8.4 Pediatric Use**

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

**8.5 Geriatric Use**

In PIIMA, 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 (CrCl: 60 to 89 mL/min) to moderate (CrCl: 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]

**17 PATIENT COUNSELING INFORMATION**

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

**8.6 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:** Neutropenia

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

**Skin and Subcutaneous Tissue Disorders:** Photosensitivity.

**Vascular Disorders:** Hypertensive crisis.
Treatment Paradigms Are Shifting for Locally Advanced HPV-Positive Head and Neck Cancers

by KAVEH ZAKERI, MD, MAS; AND NANCY Y. LEE, MD

THE STANDARD OF CARE for patients with locally advanced head and neck squamous cell carcinomas does not substantially differ according to human papillomavirus (HPV) status in the National Comprehensive Cancer Network guidelines.1 Resectable tumors can be treated with surgery followed by adjuvant therapy. Alternatively, definitive chemoradiation therapy with cisplatin is the other dominant treatment paradigm. Incidence of HPV-associated oropharyngeal squamous cell carcinoma has increased rapidly and is associated with higher overall survival (OS) compared with cancers caused by smoking and alcohol.2,3 Given the unique biology of HPV-associated oropharyngeal disease, a separate staging system was developed for these tumors.4

HPV-associated oropharyngeal cancers are more radiosensitive and chemosensitive than cancers caused by smoking and alcohol, yet the traditional treatment paradigms—including high doses of radiation and chemotherapy—were developed prior to the epidemic of HPV-associated disease. De-escalation of therapy has been proposed for HPV-associated oropharyngeal cancer based on data demonstrating high OS and progression-free survival (PFS).5 De-escalation of therapy has been investigated for both definitive surgical and chemoradiation therapy paradigms. Most de-escalated approaches focus on selecting patients according to clinical features, such as disease stage and smoking status, whereas personalized de-escalation reduces treatment intensity for patients according to treatment response.

TRANSORAL ROBOTIC SURGERY FOLLOWED BY ADJUVANT RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

Transoral robotic surgery (TORS) is a minimally invasive approach that reduces morbidity compared with traditional, open surgery for patients with oropharyngeal cancers. TORS is a standard of care option for patients with resectable tonsil or base of tongue tumors when adequate functional outcome can be preserved. For patients with HPV-associated oropharyngeal disease, postoperative radiation is typically recommended for those with high-risk features including close or positive margins, lymphovascular invasion, perineural invasion, and involved lymph nodes. Adjuvant chemotherapy is recommended for patients with positive margins or lymph nodes with extracapsular extension. Standard doses of radiation consist of 50 to 60 Gy; standard adjuvant chemotherapy typically includes either high-dose or weekly cisplatin.

De-escalated postoperative treatment has been investigated, including reduced intensity of radiation and/or chemotherapy. De-escalation of adjuvant radiation therapy has involved both reduced dose and target volumes. ECOG-ACRIN 3311 (NCT01898494) was a randomized clinical trial in which investigators evaluated reduced dose adjuvant radiation therapy for patients with intermediate postoperative risk factors.6 Patients with low-risk pT1-T2, N0-1 disease with negative margins were observed. Patients with intermediate risk disease (close margins, <1 mm of extranodal extension, 2 to 4 involved lymph nodes, perineural invasion, or lymphovascular invasion) were randomized to postoperative radiation of either 50 or 60 Gy. High-risk patients with positive margins, greater than 1 mm of extranodal extension, or more than 5 involved nodes received radiation with cisplatin. At a median follow-up of 35.1 months, the 3-year PFS rates were 96.9%, 94.9%, 93.5%, and 90.7% for the low-risk, 50 Gy, 60 Gy, and high-risk arms, respectively.6

Reduced doses of postoperative radiation and chemotherapy were also investigated in the single-arm MC1273 clinical trial (NCT01932697).7 Following surgery, patients received 30 to 36 Gy in 1.5-Gy twice-daily fractions with weekly docetaxel chemotherapy. The rates of 2-year locoregional control, PFS, and OS were 96.2%, 91.1%, and 98.7%, respectively, with 3 years of follow-up. The intensity of 30 to 36 Gy given twice daily compared with the standard 50 to 60 Gy given once daily is unclear.8 Randomized clinical trials are needed to determine whether the MC1273 treatment regimen results in noninferior cure rates with reduced toxicity compared with standard therapy.

The PATHOS trial (NCT02215265) is an ongoing randomized clinical trial investigating a reduction in adjuvant radiation and chemotherapy.9 Patients with low-risk disease are observed postoperatively,
patients with intermediate risk factors are randomized to 50 Gy vs 60 Gy, and patients with high-risk features are randomized to 60 Gy alone or 60 Gy with cisplatin.

An additional postoperative de-escalation strategy involves omission of the primary site (tonsil or base of tongue) for patients without primary site risk factors for recurrence (perineural invasion, lymphovascular invasion, or close surgical margins).10 The AVOID trial (NCT02159703) was a single-arm study of adjuvant radiotherapy to the neck alone in patients without primary site risk factors. In total, 60 patients were enrolled and at 2.4 years of median follow-up, only 1 patient had a primary site recurrence. Although this strategy appears promising, more work is necessary to validate these findings and determine the long-term risks and benefits of this approach.

Collectively, these clinical trials demonstrate that TORS followed by adjuvant radiation with or without chemotherapy results in high rates of tumor control. Reduced doses of postoperative radiation and chemotherapy appear promising as a strategy to reduce toxicity while maintaining high rates of cure, and clinical trials investigating these approaches are ongoing.

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<th>COMPARISON OF SURGERY WITH RADIATION-BASED TREATMENT</th>
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Two randomized clinical trials have compared TORS plus adjuvant therapy with definitive chemoradiation—the ORATOR trial (NCT01590355) and the ORATOR2 trial (NCT03210103).11,12 The phase 2 ORATOR trial was designed to determine whether TORS would improve 1-year swallowing quality of life. After 25 months of follow-up, patients treated with radiation had a statistically significant improvement in swallowing quality of life, but the difference did not meet the prespecified threshold of clinical significance. There was no difference in PFS or OS between the groups.

The follow-up ORATOR2 study randomized patients to de-escalated radiation-based treatment vs surgery with de-escalated adjuvant therapy.12 The results are pending release. Additional studies are needed to determine the differences between surgery and radiation-based paradigms for treatment of HPV-associated oropharyngeal disease.

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<th>DEFINITIVE RADIATION WITH CHEMOTHERAPY, CETUXIMAB, AND/OR IMMUNOTHERAPY</th>
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Definitive radiotherapy with high-dose cisplatin is the alternative to TORS-based approaches and is standard for unresectable HPV-associated oropharyngeal tumors. In an attempt to reduce the toxicity of treatment, cetuximab (Erbitux) was proposed as an alternative to cisplatin chemotherapy. Three randomized phase 3 trials compared cisplatin/radiotherapy with cetuximab/radiotherapy: RTOG 1016 (NCT01302834), De-ESCALaTE HPV (NCT01874171), and TROG 12.01 (NCT01855451). Investigators of all 3 trials observed a statistically significant detriment in either PFS or OS for patients treated with cetuximab/radiotherapy (TABLE). Additionally, toxicity was
These randomized clinical trials highlight the importance of radiosensitizing cisplatin in combination with radiation therapy. Replacement of cisplatin with cetuximab and omission of cisplatin led to inferior tumor control without improvements in toxicity. For patients with high-risk disease, immunotherapy has not demonstrated a benefit when added to cisplatin/radiation or radiation/cetuximab. For patients with favorable-risk disease, ongoing clinical trials will determine whether there is a role for radiation/immunotherapy.

PERSONALIZED CHEMORADIATION THERAPY BASED ON HYPOXIA IMAGING

Personalized treatment strategies involve tailoring the intensity of radiation and chemotherapy to individual patient biology and tumor response. Among patients with HPV-associated oropharyngeal cancer, there is heterogeneity in tumor biology and resistance to treatment. Replacement of cisplatin with cetuximab or omission of cisplatin with 5-fluorouracil could result in successful de-escalation. Patients had resection of the primary tumor prior to chemoradiation and planned neck dissection at 4 months post chemoradiation to measure pathologic response. Patients with resolution of hypoxia on 18F-FMISO PET imaging were treated to 30 Gy with 2 cycles of chemotherapy. Among the 19 enrolled patients, the 2-year rates of locoregional control and OS were 94.4% and 94.7%, respectively.29

Phase 2 of the 30 ROC trial examined the same strategy of resection of the primary tumor followed by 30 Gy of radiation and 2 cycles of chemotherapy with omission of planned neck dissections. The rates of 1-year locoregional control, distant metastasis-free survival, and OS were 94%, 100%, and 100%, respectively, at median follow-up of 1 year.30 All 8 reported local recurrences were in the neck and successfully salvaged with surgery. A subsequent phase of the 30 ROC trial is ongoing with omission of both resection of the primary tumor and planned neck dissection.

NEXT STEPS FOR PATIENTS WITH HEAD AND NECK CANCERS

The standard-of-care treatment paradigms for patients with locally advanced HPV-associated head and neck cancer include up-front surgery followed by adjuvant radiation with or without chemotherapy and definitive radiation with cisplatin. De-escalation of postoperative adjuvant therapy is the subject of investigation. Replacement of cisplatin with cetuximab or omission of cisplatin with definitive radiotherapy have not been successful. The addition of immunotherapy to definitive radiation-based treatment has not demonstrated a benefit thus far. A personalized treatment paradigm based on hypoxia imaging is promising and may yield a successful, personalized de-escalation strategy for patients with HPV-associated oropharynx cancer.

For a full list of references, see the article at OncLive.com.
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®.Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS
The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions.

Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS
CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS
Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib) capsules, for oral use

INDICATIONS AND USAGE
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system event; e.g., intracranial hemorrhage including subdural hematoma), gastrointestinal bleeding, hematoma, and post procedural hemorrhage occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively. The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending on the type of surgery and the risk of bleeding [see Clinical Studies (14) in Full Prescribing Information].

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,478 patients who received IMBRUVICA in clinical trials [see Adverse Reactions]. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci/pneumonia (PJ/P) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 22% of patients. Grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA. Grade 3 or greater ventricular tachycardias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias [see Adverse Reactions]. At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Dosage and Administration (2.2) in Full Prescribing Information].

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

IMBRUVICA® (ibrutinib)

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-30 times higher than those reported in patients with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. [see Use in Specific Populations].

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

• Hemorrhage [see Warnings and Precautions]
• Infections [see Warnings and Precautions]
• Cytopenias [see Warnings and Precautions]
• Cardiac Arrhythmias and Cardiac Failure [see Warnings and Precautions]
• Hypertension [see Warnings and Precautions]
• Second Primary Malignancies [see Warnings and Precautions]
• Tumor Lysis Syndrome [see Warnings and Precautions]

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to IMBRUVICA in 6 trials as a single agent at 420 mg orally once daily in 475 patients and at 560 mg orally once daily in 174 patients and in 4 trials administered in combination with other drugs at 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies who received IMBRUVICA, 87% were exposed for 6 months or longer and 68% were exposed for greater than one year. In this pooled safety population of 1,476 patients with B-cell malignancies, the most common adverse reactions (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure to IMBRUVICA in one single-arm, open-label clinical trial (Study 1102) and five randomized controlled clinical trials (RESONATE, RESONATE-2, HELIOS, ILLUMINATE, and E1912) in patients with CLL/SLL (n=2,016 total, including n=1,133 patients exposed to IMBRUVICA). In general, patients with creatinine clearance (Clcr) ≥ 30 mL/min, AST or ALT ≥ 2.5 x ULN, or total bilirubin ≥ 1.5 x ULN (unless of non-hepatic origin) were excluded from these trials. In Study E1912, patients with AST or ALT > 3 x ULN or total bilirubin > 2.5 x ULN were excluded. Study 1102 included 51 patients with previously treated CLL/SLL. RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab. RESONATE-2 included 267 randomized patients with treatment naive CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil. HELIOS included 274 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with BR or placebo in combination with BR. ILLUMINATE included 228 randomized patients with treatment naive CLL/SLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab. E1912 included 510 patients with previously untreated CLL/SLL who were 70 years or younger and received IMBRUVICA in combination with rituximab or received fludarabine, cyclophosphamide, and rituximab (FCR).

The most common adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥ 30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising, and nausea. Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, neutropenia, arthralgia, rash, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in approximately 9% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from Study 1102 (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 1 and 2.

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.
IMBRUVICA® (ibrutinib)

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td>Second malignancies</td>
<td>10</td>
<td>2*</td>
</tr>
</tbody>
</table>

Table 2: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Percent of Patients (N=51)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

RESOLUTE-2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 11 months in RESOLUTE-2.
Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*Includes multiple ADR terms
### Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

† Includes one event with a fatal outcome.

**E1912:** Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.

### Table 9: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912 (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>Constipation</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>61</td>
<td>5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>49</td>
<td>4</td>
</tr>
<tr>
<td>Bruising*</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Peri neuralgia</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>16</td>
<td>1</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

**Table 10:** Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Hematology abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>AST increased</td>
<td>25</td>
<td>3</td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria.
Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 6.4% versus 1.8% and for Grade 3 or greater was 4.0% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of cardiac failure of any grade was 1.7% versus 0.5% and for Grade 3 or greater was 1.2% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) of any grade was 0.4% versus 0.3% and Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,605 of these patients, the median time to first onset was 3 days (range, 1 to 79 days), with a median duration of 4 days (range, 0 to 118 days) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 65) versus 4 days (range, 1 to 267) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 58) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 16% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 0% in the control arm (5% Grade 1 and <1% Grade 2 and 3). Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 617) versus 105 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of IMBRUVICA. 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.

- **Hepatotoxicity**: hepatitis failure including acute and/or fatal events, hepatic cirrhosis
- **Gastrointestinal disorders**: interstitial lung disease
- **Metabolic and nutrition disorders**: tumor lysis syndrome
- **Immune system disorders**: anaphylactic shock, angioedema, urticaria
- **Skin and subcutaneous tissue disorders**: Stevens-Johnson Syndrome (SJS), anoxychosis, panniculitis, neutrophilic dermatoses
- **Infections**: hepatitis B reactivation
- **Nervous system disorders**: peripheral neuropathy

**DRUG INTERACTIONS**

**Effect of CYP3A Inhibitors on Ibrutinib**: The coadministration of IMBRUVICA with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. If these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

**Effect of CYP3A Inducers on Ibrutinib**: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**: Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities (see Data). Advise pregnant women of the potential risk to a fetus.

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

**Data**: Animal Data: ibrutinib was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MZL) and 20 times the exposure in patients with CLL/SLL or Waldenström’s Macroglobulinemia (WM) administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily. Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose at 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

**Contraception**: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose.

**Females and Males of Reproductive Potential**: Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating IMBRUVICA.

**Contraception**: Females: IMBRUVICA can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

**Males**: Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

**Pediatric Use**: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

**Geriatric Use**: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

**Hepatic Impairment**: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.
IMBRUVICA® (ibrutinib)

Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

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

- Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].

- Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].

- Cardiac arrhythmias and cardiac failure: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema [see Warnings and Precautions].

- Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].

- Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].

- Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].

- Embryo-fetal toxicity: Advise 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, Use in Specific Populations].

Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations].

Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations, Nonclinical Toxicology (13.1) in Full Prescribing Information].

- Lactation: Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose [see Use in Specific Populations].

- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].

- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

- Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].

- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

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Practice-Changing Data From 2021 Sets Tone for New Year
by ONCLIVE® STAFF

THROUGHOUT 2021, INVESTIGATORS
of several pivotal trials presented findings that may result in shifting standards for the treatment of patients across tumor types. Published papers and presentations at several key meetings generated debates in sequencing and sparked conversations on where the next areas of opportunities exist to refine personalized therapies.

Further, as investigators announced confirmatory and preliminary findings for several trials, the FDA issued approvals that expanded the use of agents such as pembrolizumab (Keytruda) and welcomed others such as sotorasib (Lumakras) into the landscape.

The editors of OncologyLive® spoke with key opinion leaders who highlighted some of the most pivotal data that pave the way for change in the coming year.

BREAST CANCER
Fam-trastuzumab deruxtecan-nxki (Enhertu) has generated buzz for close to 2 years following the landmark data from the phase 2 DESTINY-Breast01 trial (NCT03248492). These data led to the accelerated approval of the agent for patients with advanced HER2-positive metastatic breast cancer who have received 1 or more prior anti-HER2-based regimens.

At the European Society for Medical Oncology (ESMO) Annual Congress 2021, investigators further solidified the advantage of trastuzumab deruxtecan over T-DM1 in patients previously treated with trastuzumab and taxane for HER2-positive metastatic breast cancer, said Virginia Kaklamani, MD. “Trastuzumab deruxtecan demonstrated a highly statistically significant and clinically meaningful improvement in PFS vs T-DM1 in patients previously treated with trastuzumab and taxane for HER2-positive metastatic breast cancer,” said Kaklamani, who is professor of medicine in the division of hematology/oncology at University of Texas (UT) Health San Antonio and is the leader of the Breast Cancer Program at UT Health San Antonio MD Anderson Cancer Center.

Patients were randomized 1:1 and the primary end point was progression-free survival (PFS) by blinded independent central review. The median PFS was not reached (95% CI, 18.5-not estimable [NE]) in the trastuzumab deruxtecan arm vs 6.8 months (95% CI, 5.6-8.2) in the T-DM1 arm (HR, 0.28; 95% CI, 0.22-0.37; \( P = 7.8 \times 10^{-22} \)).

Further, the estimated 12-month overall survival (OS) event rates were 94.1% (95% CI, 90.3%-96.4%) vs 85.9% (95% CI, 80.9%-89.7%), respectively. Similar rates of treatment-emergent adverse effects were observed, and no drug-related deaths occurred in either arm. Adjudicated drug-related ILD occurred in 10.5% of patients with trastuzumab deruxtecan vs 1.9% with T-DM1. Investigators concluded that these
data present an unanswered clinical question regarding sequencing of the agent among other HER2-targeting agents.

For more from DESTINY-Breast03, visit bit.ly/3nksC1.

Pembrolizumab (Keytruda) plus chemotherapy with or without bevacizumab (Avastin) resulted in a statistically significant and clinically meaningful improvement in OS and PFS in patients with persistent, recurrent, or metastatic cervical cancer, according to Bradley J. Monk, MD, FACS, FACOG, who added that next steps will examine the addition of checkpoint inhibitors to chemotherapy and radiation.

Results from the phase 3 KEYNOTE-826 (NCT04221945) showed that pembrolizumab plus chemotherapy with or without bevacizumab resulted in a median PFS of 10.4 months (95% CI, 9.1-12.1) vs 8.2 months (95% CI, 6.4-8.4) with chemotherapy with or without bevacizumab in the all-comer population (HR, 0.79; 95% CI, 0.65-0.92; P = .0002). The median OS was 24.4 months (95% CI, 19.2-not reached) in the investigative arm vs 16.5 months (95% CI, 14.5-19.4) in the control arm (HR, 0.67; 95% CI, 0.54-0.84; P < .001). The agent was approved based on these data in October.

"[Other efforts are now adding] checkpoint inhibitors, such as pembrolizumab, to chemotherapy and radiation, [such as the] phase 3 study called KEYNOTE-818 [NCT04221945]," said Monk who is a professor in the Division of Gynecologic Oncology at Arizona Oncology, University of Arizona College of Medicine, Creighton University School of Medicine at St Joseph's Hospital; medical director of the Gynecologic Program of the US Oncology Research Network; and co-director of GOG Partners. "Hopefully, [with this approach, we will] cure more patients, which is really what we’re trying to do," Monk said. “I like helping [patients] live longer and I like helping them feel better, but really, the goal is to cure patients which is what the other sponsor is doing with durvalumab [Imfinzi]. Two studies are now examining frontline chemotherapy and radiation.”

For more from Monk on KEYNOTE-826, visit bit.ly/3owtxZT.

The combination of nivolumab (Opdivo) and chemotherapy has shown a significant benefit across outcomes for patients with gastric cancer and results from the phase 3 CheckMate 649 trial (NCT02872116) solidified its role in the treatment paradigm. On April 16, 2021, the FDA approved the PD-1-blocking antibody in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer (GEJC), and esophageal adenocarcinoma.

Data from the trial showed that patients treated with the combination of nivolumab and either FOLFOX (folinic acid, fluorouracil and oxaliplatin) or CapeOX (capecitabine plus oxaliplatin) chemotherapy achieved a median OS of 13.8 months (95% CI, 12.6-14.6) in 789 patients, compared with 11.6 months (95% CI, 10.9-12.5) in 792 patients treated with chemotherapy alone (P = .0002). The overall response rates were 47% (95% CI, 43%-50%) vs 37% (95% CI, 34%-40%), respectively.

"Incidentally, this was not the primary end point of this study when it was initially designed; this was [adjusted] during the study as more data came in. The primary end point is PFS and OS for CPS 5 or higher. There were 2 other groups: CPS 1 to 4 and all patients," said Jaffer A. Ajani, MD, a professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston. "There were a series of prior studies before this which already demonstrated that PD-L1 expression makes a difference. If [a patient is] PD-L1 positive, irrespective of the number, it makes a difference. Looking at the survival curves, there is benefit [seen across groups] and the maximum benefit was for those with CPS of 5 or higher for PFS and OS; this was a considerable benefit. The median survival difference was more than 3 months. You don't get that with gastric cancer very often, and PFS is approximately 1.6 months. The P values are very strong. [These data] have been practice changing. There are further studies that are looking to see if that space can be further elaborated on, but the best evidence we have right now [for this combination] is from CheckMate 649.”

For more on CheckMate 649, visit bit.ly/3kJTnSF.

Radiopharmaceuticals are making headway as treatment options in metastatic castration-resistant prostate cancer (mCRPC) with lutetium 177 (177Lu)-PSMA-617 leading the pack in 2021.

Findings from the phase 3 VISION trial (NCT03511664) showed that at a median follow-up of 20.9 months, the addition of 177Lu PSM617 the median OS was...
15.3 months in the investigational arm vs 11.3 months in the standard-of-care arm (HR, 0.62; 95% CI, 0.52-0.74; P < .001). The radiographic PFS was 8.7 vs 3.4 months, respectively (HR, 0.40; 99.2% CI, 0.29-0.57; P < .001).

“This study involved patients who had mCRPC who had progressed on at least 1 novel hormonal agent, and at least 1 taxane-based therapy,” said Neal Shore, MD, US Chief Medical Officer of Surgery and Oncology at GenesisCare USA, and director at Carolina Urologic Research Center in Myrtle Beach, South Carolina. “Many of these patients had had multiple taxane therapies and multiple novel hormonal agents. These patients had high tumor burden [and] had progressed on numerous lines of therapy yet were highly motivated to be randomized to receive 177Lu-PSMA-617.”

“The VISION trial wonderfully demonstrated the benefit of delaying disease progression by rPFS monitoring, as well as an HR and a survival benefit of approximately 0.6, which is important because its unique mechanism of action supplements the already approved unique mechanisms of action of androgen receptor pathway inhibitory drugs, taxanes, other radiopharmaceuticals such as radium-223 dichloride [Xojogo], and even immunotherapeutics. This is extremely important. This study will clearly lead to additional trials, looking in the prechemotherapy mCRPC and metastatic castration-sensitive prostate cancer populations. Assuredly, there will be other radioisotopes that can be linked to antibodies that will add to the opportunities for trials, research, and therapeutic awareness throughout the prostate cancer journey.”

In September, the FDA granted priority review to the application for 177Lu-PSMA-617.

For more on the VISION trial, visit bit.ly/312DzL9.

Results of IMpower010 (NCT02486718), presented at several meetings and most recently published in the Lancet, generated discussions on the role of adjuvant atezolizumab (Tecentriq) over best supportive care for patients with non–small cell lung cancer (NSCLC), specifically in those with earlier-stage disease (IB-IIIA).

Improved disease-free survival (DFS) data suggest that patients treated with adjuvant atezolizumab after adjuvant chemotherapy with PD-L1 expression greater than 1%. At a median follow-up of 32.8 months, the median DFS for those who had received atezolizumab was NE (95% CI, 36.1-NE) compared with 35.3 months (95% CI, 29.0-NE) in those who received best supportive care (HR, 0.66; 95% CI, 0.50-0.88; P = .004).

“The benefit was extended to all randomized patients in the intention-to-treat population. The median DFS for those in the atezolizumab arm was NE (95% CI, 36.1-NE) versus 37.2 months (95% CI, 31.6-NE) in the best supportive care arm (HR, 0.81; 95% CI, 0.67-0.99; P = .04).”

“Looking at immunotherapy for patients with completely resected NSCLC after chemotherapy and immunotherapy has been a transformative treatment for metastatic lung cancer,” said Stephen V. Liu, MD. “We also know that for patients with resected lung cancer, while our goal is cure, it’s not always our expectation. Lung cancer is a very difficult disease to eradicate.” Liu is an associate professor of medicine, director of thoracic oncology and director of developmental therapeutics at the Lombardi Comprehensive Cancer Center of Georgetown University in Washington, DC.

The relapse rate for patients treated with curative intent is approximately 60%, and for those treated earlier in their disease course, immunotherapy may reduce incidence of recurrence. “Implementing immunotherapy in that setting really can improve our outcomes and extend the cure to more people coupled with earlier detection and screening,” Liu said. “I think this has a chance to make a huge impact for patients with lung cancer.”

The FDA approved adjuvant atezolizumab following resection and platinum-based chemotherapy for patients with stage II to IIIA disease with a PD-L1 expression of at least 1% in October.

For more on IMpower010, visit bit.ly/3wU1v01.

Approvals in hematologic malignancies for the 2021 calendar year included the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy brexucabtagene autoleucel (Tecartus) for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Data from the phase 2 ZUMA-3 trial (NCT02614066) presented at the 2021 American Society of Clinical Oncology Annual Meeting and later published in The Lancet, showed that treatment with the product elicited complete remission (CR) or complete remission with incomplete hematological recovery (CRI) among 70.9% of treated patients. This included a CR rate of 56.4%. As of the data cutoff, 31% of patients who achieved a CR/CRI were in ongoing remission without subsequent allogeneic stem cell transplant.

The median duration of response with censoring at subsequent allogeneic stem cell transplant, relapse-free survival, and overall survival (OS) was 12.8 months (95% CI, 8.7-NE), 11.6 months (95% CI, 2.7-15.5), and 18.2 months (95% CI, 15.9-NE), respectively. The median OS was not reached in patients who achieved CR/CRI with the CAR T-cell therapy.

“The [reported] median OS was outstanding; 18.2 months for the group,” said Bijal Shah, MD, MS, an associate member in the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida. “In those who achieved a CR or CRI, we haven’t yet reached median survival estimate. For the types of patients we enrolled, recognizing many had seen prior inotuzumab ozogamicin (Besponsa) or prior blinatumomab (Blincyto), transplant and the like, these data are quite remarkable.”

For more on the approval of brexucabtagene autoleucel, visit bit.ly/3COQmrl.
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Checkpoint Blockade Moves Needle in Molecularly Driven Endometrial Cancer Paradigm

by GINA MAURO

SIGNIFICANT PROGRESS IN THE treatment of patients with endometrial cancer is reflected in the wave of recent wave of FDA approvals of checkpoint inhibitors alone and in combination, said Bhavana Pothuri, MD, MS, in a presentation during the 39th Annual Chemotherapy Foundation Symposium (CFS®): Innovative Cancer Therapy for Tomorrow®, hosted by Physicians’ Education Resource® (PER®), LLC.¹ Ongoing investigative efforts in this molecularly driven malignancy have transformed the treatment landscape, providing individualized paths forward for many patients.

“The treatment paradigm [for endometrial cancer] has changed significantly and will continue to evolve,” said Pothuri, a professor in the Department of Obstetrics and Gynecology and Medicine at NYU Grossman School of Medicine and director of Gynecologic Oncology Clinical Trials at NYU Langone Health’s Laura and Isaac Perlmutter Cancer Center in New York, New York.

Endometrial cancer cancers are stratified into 4 distinct subtypes: POLE-mutant, microsatellite instability–high (MSI-H)/mismatch repair deficient (dMMR), copy number (CN) low, and CN high/TP53 abnormal. Patients with POLE-mutant disease tend to have the best prognosis compared with those who have CN-low or MSI-H/dMMR disease (intermediate outcomes), and CN-high/TP53 abnormal disease (worst prognosis).²

Until 2017, the sole FDA-approved therapy in the endometrial cancer armamentarium was megestrol acetate. Clinical practice now benefits from 3 new regimens available based on patients’ molecular profiles: pembrolizumab (Keytruda), dostarlimab-gxly (Jemperli), and pembrolizumab plus lenvatinib (Lenvima).

RECENT REGULATORY ADVANCES IN ENDOMETRIAL CANCER TREATMENT

MSI-H/dMMR: Pembrolizumab

Pembrolizumab was explored in the open-label, nonrandomized, phase 2 KEYNOTE-158 trial (NCT02628067), which evaluated the PD-1 inhibitor as a single agent in previously treated patients with advanced MSI-H/dMMR tumors, including endometrial cancer. Patients received either pembrolizumab at 200 mg every 3 weeks or at 10 mg/kg every 2 weeks.

Preliminary findings from all-comers showed that the objective response rate (ORR) among 149 patients was 39.6% (95% CI, 31.7%-47.9%), and responses lasting at least 6 months occurred in 78% of responders.³

The FDA granted a tissue-agnostic approval in May 2017 to pembrolizumab based on the preliminary KEYNOTE-158
data, making it the first regulatory approval based on a biomarker regardless of tumor type.3

Longer follow-up data of the endometrial cancer cohort were presented at the European Society of Medical Oncology Congress 2021. At the data cutoff of October 5, 2020, the ORR in the efficacy-evaluable population of the endometrial group (cohorts D and K; n = 79) was 48% (95% CI, 37%-60%), which included a 14% complete response (CR) rate and a 34% partial response (PR) rate; 18% of patients had stable disease.

The median time to response was 2.3 months (range, 1.3-10.6). Additionally, the median duration of response (DOR) had not been reached, but investigators reported that 68% of patients maintained a response at 3 years. The median progression-free survival (PFS) and overall survival (OS) were 13.1 months (95% CI, 4.3-34.4) and not reached (NR; 95% CI, 27.2-NR), respectively.

Safety with pembrolizumab was consistent with that of other checkpoint inhibitors. Treatment-related adverse events (TRAEs) occurring in at least 10% of patients included pruritis (24%), fatigue (21%), diarrhea (16%), arthralgia (14%), nausea (14%), hypothyroidism (13%), and rash (11%). Immune-related AEs (irAEs) at any grade occurred in 28% of patients; 7% of patients experienced these as grade 3/4 events, including colitis (n = 1), severe skin reactions (n = 2), type 1 diabetes mellitus (n = 1), hepatitis (n = 1), and adrenal insufficiency (n = 1).

**MSI-H/dMMR: Dostarlimab**

The multicenter, single-arm, multiple parallel-cohort, open-label, phase 1b GARNET trial (NCT02715284) evaluated single-agent dostarlimab, a PD-1 inhibitor, in expansion cohorts across multiple tumor types, including endometrial cancer. Patients were treated with intravenous (IV) dostarlimab at 500 mg every 3 weeks for 4 cycles followed by 1000 mg IV every 6 weeks until disease progression.

The trial featured dose-finding (part 1), fixed-dose safety run-in (part 2A), and expansion cohorts (part 2B). The expansion cohort consisted of 5 groups: dMMR endometrial cancer, mismatch repair proficient (pMMR) endometrial cancer, non–small cell lung cancer, nonendometrial dMMR/MSI-H cancer, and platinum-resistant ovarian cancer.

Dostarlimab elicited a 42.3% ORR in 71 patients with dMMR recurrent or advanced endometrial cancer, which included a 12.7% CR rate and a 29.6% PR rate.3 The DOR was at least 6 months for 93.3% of responders, and the median DOR was not reached at a median follow-up of 14.1 months (range, 2.6-22.4+). At a median follow-up of 16.5 months, the ORR via investigator-assessed irRECIST criteria was 45.5% in patients with dMMR endometrial cancer (n = 110).6

Based on the GARNET findings, the FDA granted an accelerated approval in April 2021 to dostarlimab for the treatment of patients with recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing chemotherapy and whose cancers are dMMR, as determined by an FDA-approved test.7

The safety profile with dostarlimab was also found to be manageable. Any-grade treatment-emergent AEs (TEAEs) occurred in 69.9% of patients; grade 3 or higher irTEAEs had an incidence of 1.6% or lower. Additionally, increased alanine aminotransferase led to discontinuation in 1.4% of patients, but no TRAEs led to death.6

**Microsatellite Stable/pMMR: Pembrolizumab/Lenvatinib**

The combination of pembrolizumab and lenvatinib was tested in patients with advanced endometrial cancer who received prior platinum-based chemotherapy in the phase 3 KEYNOTE-775 trial (NCT03517449).

At a median follow-up of 11.4 months and in those with microsatellite stable (MSS)/pMMR disease, the median OS was 17.4 months (95% CI, 14.2-19.9) with pembrolizumab/lenvatinib vs 12.0 months (95% CI, 10.8-13.3) with chemotherapy (HR, 0.68; 95% CI, 0.56-0.84; P < .0001).8

Results showed that the median PFS in

<TABLE> Ongoing Phase 3 Trials for Patients With Advanced Endometrial Cancer

<table>
<thead>
<tr>
<th>Trial (ClinicalTrials.gov identifier)</th>
<th>Intervention</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUBY part 1 (NCT03981796)³</td>
<td>Dostarlimab plus carboplatin and paclitaxel followed by dostarlimab vs placebo plus carboplatin and paclitaxel followed by placebo</td>
<td>Primary: PFS, Select secondary: OS, ORR, DOR, DCR, PROs</td>
</tr>
<tr>
<td>RUBY part 2 (NCT03981796)</td>
<td>Dostarlimab plus carboplatin and paclitaxel followed by dostarlimab plus niraparib vs placebo plus carboplatin and paclitaxel followed by placebo</td>
<td>Primary: PFS, Select secondary: OS, ORR, DOR, DCR, PROs</td>
</tr>
<tr>
<td>AtTEnd (NCT03603184)</td>
<td>Atezolizumab plus paclitaxel and carboplatin vs paclitaxel and carboplatin</td>
<td>Primary: OS, PFS, Select secondary: ORR, DOR, AEs</td>
</tr>
<tr>
<td>NRGY018 (NCT03914612)</td>
<td>Pembrolizumab, paclitaxel, and carboplatin vs paclitaxel and carboplatin</td>
<td>Primary: PFS, Select secondary: AEs, ORR, DOR</td>
</tr>
<tr>
<td>KEYNOTE-B21 (NCT04634877)</td>
<td>Pembrolizumab with adjuvant chemotherapy with or without radiotherapy vs placebo with adjuvant chemotherapy with or without radiotherapy</td>
<td>Primary: DFS, OS, Select secondary AEs</td>
</tr>
<tr>
<td>LEAP-001 (NCT03884101)</td>
<td>Pembrolizumab plus lenvatinib vs paclitaxel plus carboplatin</td>
<td>Primary: OS, PFS, Select secondary: ORR, AEs</td>
</tr>
</tbody>
</table>

*Enrollment is complete.

AEs, adverse events; DCR, disease control rate; DFS, disease-free survival; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes.
patients with pMMR status was 6.6 months (95% CI, 5.6-7.4) and 3.8 months (95% CI, 3.6-5.0) with pembrolizumab/lenvatinib and chemotherapy, respectively (HR, 0.60; 95% CI, 0.50-0.72; \( P < .0001 \)). The ORR was 30.3% (95% CI, 25.5%-35.5%) with pembrolizumab/lenvatinib vs 15.1% (95% CI, 11.5%-19.3%) with physician’s choice; the median DOR was 9.2 months (range, 1.6-23.7) vs 5.7 months (range, 0.0-24.2), respectively.

In all-comers, the median OS was 18.3 months (95% CI, 15.2-20.5) and 11.4 months (95% CI, 10.5-12.9), respectively (HR, 0.62; 95% CI, 0.51-0.75; \( P < .0001 \)). The median PFS was 7.2 months (95% CI, 5.7-7.6) with pembrolizumab/lenvatinib and 3.8 months (95% CI, 3.6-4.2) with chemotherapy (HR, 0.56; 95% CI, 0.47-0.66; \( P < .0001 \)). The ORRs were 31.9% (95% CI, 27.4%-36.6%) and 14.7% (95% CI, 11.4%-18.4%) with pembrolizumab/lenvatinib and physician’s choice, respectively. Finally, the median DOR was 14.4 months (range, 1.6-24.2) and 5.7 months (range, 0.0-24.2).\(^8\)

Results of a subgroup analysis from KEYNOTE-775 demonstrated the improvement of pembrolizumab/lenvatinib over physician’s choice of therapy in patients with dMMR endometrial cancer. The median OS was not reached (NR; 95% CI, NR-NR) with pembrolizumab/lenvatinib compared with 8.6 months (95% CI, 5.5-12.9) for physician’s choice of therapy (HR, 0.37; 95% CI, 0.22-0.62; \( P < .0001 \)).\(^8\)

Here, the median PFS was 10.7 months (95% CI, 5.6-NR) and 3.7 months (95% CI, 3.1-4.4), respectively (HR, 0.36; 95% CI, 0.23-0.57; \( P < .0001 \)). The ORRs were 40.0% (95% CI, 28.0%-52.9%) and 12.3% (95% CI, 5.5%-22.8%), respectively.

The combination was given accelerated approval in September 2019, followed by a regular approval in July 2021, for use in patients with advanced endometrial carcinoma that is not MSI-H/dMMR, who have disease progression following prior systemic therapy in any setting, and who are ineligible for curative surgery or radiation.\(^9\)

Regarding safety, toxicities associated with pembrolizumab/lenvatinib were consistent with those observed with each therapy given individually. The most frequent all-grade and grade 3 or higher TEAEs included hypertension (64% and 38%, respectively), hypothyroidism (all-grade, 57%), diarrhea (54% and 8%, respectively), nausea (all-grade, 50%), and decreased appetite (45% and 8%, respectively).\(^8\)

Additional grade 3 or higher TEAEs with the combination included weight decrease (10%), anemia (6%), asthenia (6%), fatigue (5%), and proteinuria (5%). It should be noted that 5.7% of patients on pembrolizumab/lenvatinib died as a result of grade 5 gastrointestinal disorders (1.2%); cardiac disorders (0.5%); general disorders (1.5%); infections (0.7%); neoplasms, nervous system, psychiatric, renal, reproductive, or respiratory disorders (0.2% each); and decreased appetite (0.2%). This was compared with 4.9% of patients on the physician’s choice arm.\(^8\)

“There are overlapping toxicities to also keep in mind with the diarrhea and the hypothyroidism,” Pothuri said. “It’s important to sort out [whether] those [are] related to the immunotherapy or to the lenvatinib.”

**FUTURE BIOMARKER-DRIVEN DEVELOPMENTS**

Investigators of ongoing phase 3 trials are evaluating more immune-based combinations with chemotherapy, PARP inhibitors, and other novel agents as possible treatments for select subsets of patients with endometrial cancer (TABLE). Investigators of 2 trials that enrolled patients with CN-low and CN-high disease have presented data that point toward improved outcomes with CDK4/6 inhibitors and HER2-targeted agents.

**CN-Low Disease**

Although patients with endometrial cancer with CN-low disease have long been treated with chemotherapy, Pothuri says this likely is not the optimal approach for this subset. The phase 2 ENGOT-EN3-NSGO/PALEO study (NCT02730429) enrolled patients with primary stage IV or relapsed measurable/evaluable endometrial cancer who have received at least 1 prior systemic therapy. Patients were randomized 1:1 to receive palbociclib (Ibrance) at 125 mg on days 1 to 21 plus letrozole at 2.5 mg on days 1 to 28 vs placebo and letrozole at the same dosage schedule every 28 days until disease progression. The primary end point was investigator-assessed PFS.\(^10\)

Data showed that the median PFS was 9.2 months and 6.0 months, respectively, with palbociclib/letrozole and placebo/letrozole, respectively (HR, 0.49; 90% CI, 0.25-0.97; \( P = .005 \)).\(^11\) In patients with primary stage III to IV disease, the median PFS was 17.9 months and 9.3 months, respectively (HR, 0.40; 90% CI, 0.20-0.80; 1-sided \( P = .013 \)). For those with recurrent disease, the median PFS was 9.2 months and 6.0 months, respectively (HR, 0.14; 90% CI, 0.04-0.53; \( P = .003 \)).

An updated analysis showed an OS benefit in the stage III to IV subgroup, in which the median OS was NR in the trastuzumab arm vs 25.4 months with chemotherapy alone (HR, 0.49; 90% CI, 0.25-0.97; \( P = .041 \)).\(^12\)

“There is lots of great interest and it is really an exciting time to be in the endometrial cancer space,” Pothuri said. “The role of trastuzumab and other HER2/neu-directed therapies for CN-high biomarker-positive tumors also needs further investigation in phase 3 trials.”
The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

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PROGRAM OVERVIEW

• Nominations are open through February 28, 2022.
• The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
• A selection Committee of more than 120 oncologists will vote to determine the 2022 inductees.
• The 2022 Giants of Cancer Care® class will be announced in Spring, 2022.
Bispecific Monoclonal Antibodies Lead Immune-Directed Therapies Into the Future

by JASON HARRIS

BISPECIFIC MONOCLONAL ANTIBODIES HAVE begun to step out as a treatment of interest across malignancies, but thus far their use in practice is limited to non–small cell lung cancer (NSCLC), leukemia, and hemophilia. However, that may change because investigative efforts into these agents are increasing rapidly and they soon may be available to treat a broad range of hematologic and solid cancers, said Steven T. Rosen, MD, during the Giants of Cancer Care® Lecture at the 39th Annual Chemotherapy Foundation Symposium (CFS®): Innovative Cancer Therapy for Tomorrow®, hosted by Physicians’ Education Resource® (PER®), LLC.

“The future is going to be very complex [and challenging] for all of us,” said Rosen, who received the 2021 Giants of Cancer Care® award for lymphoma. “Already we see the spectrum of bispecifics...being developed for blood cancers and solid tumors. How to adequately study them [and] how to decide which [is the] better [treatment option for our patients] is going to be truly challenging. But the science is there for us to rapidly develop these products.”

Three FDA-approved bispecific monoclonal antibodies are available: blinatumomab (Blincyto), which targets CD19 and CD3 in patients with acute B-cell lymphoblastic leukemia; amivantamab-vmwy (Rybrevant), which targets EGFR and MET receptors in adults with NSCLC; and emicizumab-kwxh (Hemlibra) for patients with hemophilia.1

During his presentation, Rosen discussed the evolving role of bispecific monoclonal antibodies as treatments for patients with lymphomas and how they stack up against chimeric antigen receptor (CAR) T-cell therapies. Rosen is provost and chief scientific officer, director of the Comprehensive Cancer Center and Beckman Research Institute, and the Irell & Manella Cancer Center Director’s Distinguished Chair at City of Hope in Duarte, California.

EXPANDING TREATMENT OPTIONS

Although mechanisms of action range across bispecific monoclonal antibodies, the standard construct consists of 2 binding sites directed at different targets.2 “First [comes] the engagement of the immune cells to the tumor,” Rosen said. “The antibody binds to the [natural] killer cell and binds to the tumor. The second [step] is targeted delivery of the payload where it actually binds to a toxin and brings it into the tumor or binding.”

Investigators are evaluating dozens of bispecific monoclonal antibodies, 5 of which have data reported (TABLE 1). These are odronextamab (REGN1979), mosunetuzumab (RG7828), glofitamab (RG6026), plamotamab, and epcoritamab. Similar to blinatumomab, these agents target CD19 and CD3.

Odronextamab is an IgG4-based construct. Mosunetuzumab and epcoritamab are IgG1 based and glofitamab is IgG based. Plamotamab has no Fc gamma receptor binding. All 5 agents are administered intravenously or subcutaneously.

Data collected so far show that all these agents produce impressive rates of overall response and/or complete response, some of which are comparable to approved CAR T-cell therapies. Furthermore, they do so without high rates of grade 3 or greater cytokine release syndrome (CRS), an adverse effect common to CAR T-cell therapy and antibody therapeutics.

BISPECIFIC MONOCLONAL ANTIBODIES OFFER SOME ADVANTAGES OVER CAR T CELLS

Both CAR T-cell therapies and bispecific monoclonal antibodies activate the immune system to attack cancers. Engineered CAR T cells have a long, well documented track record of improving outcomes and even inducing cures in some patients with hematologic malignancies. Furthermore, although CAR T-cell therapies are usually administered in the inpatient setting, these agents require a single application. The biggest advantage CAR T-cell therapies have now is the number of FDA-approved treatments available, Rosen said, noting that most bispecific monoclonal antibodies are investigational.

Despite the availability, there are limiting factors for CAR T-cell therapy.10 “CAR T cells require processing,” Rosen said. “[Patients need to undergo leukapheresis, [then] there are several weeks of getting the product prepared.” He added that sometimes it can be difficult to harvest CAR T cells for treatment. “The administration to

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**TABLE. Efficacy of Approved Therapies vs Investigational Agents in Lymphoma**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Approved CAR T-cell therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Axicabtagene ciloleucel</td>
</tr>
<tr>
<td>Patients with R/R DLBCL after ≥2 prior therapies</td>
<td>Patients with R/R DLBCL patients after ≥2 prior therapies</td>
</tr>
<tr>
<td>Trial (ClinicalTrials.gov identifier)</td>
<td>ZUMA-1 (NCT02348216)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>CR: 51%</td>
</tr>
<tr>
<td></td>
<td>ORR: 72%</td>
</tr>
</tbody>
</table>

ASCT, allogeneic stem cell transplant; CAR, chimeric antigen receptor; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; R/R, relapsed or refractory.
the patient [takes place], in most instances, in the hospital [and CRS] can be quite severe….Also, because there’s a delay, you often have to do with interval therapy prior to administering the CAR T.” In contrast, Rosen said bispecific monoclonal antibodies are an off-the-shelf product with no delay in treatment and little chance the therapy will not be available.

These agents have produced strong results in early testing. For example, odronextamab administered at a dose of 80 mg or higher induced an objective response rate (ORR) of 33.3% in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who previously received CAR T-cell therapy (n = 21), an extremely difficult-to-treat population. The complete remission (CR) rate was 23.8% among responders. The ORR among patients with follicular lymphoma (n = 16) treated with the same dose was 93.8% with a CR rate of 68.8%.7

Furthermore, CAR T cell agents are known to induce serious CRS and it appears the bispecific agents are safer in that respect. In the pivotal phase 2 JULIET trial (NCT02445248), the results of which led to the FDA approval for tisagenlecleucel (Kymriah), 22% of adults with relapsed/refractory DLBCL experienced grade 3/4 CRS.8

In comparison, reported incidence of grade 3/4 CRS was 7.1% with odronextamab among all 127 treated patients.7 Of the 5 bispecific monoclonal antibodies under investigation for patients with B-cell non-Hodgkin lymphoma that have gone to trial, odronextamab was the only agent with a rate of grade 3/4 CRS greater than 5%.

“Each of the constructs is different… allowing 3 different types of administration and different intervals of administration,” Rosen said. “Most importantly, look at those responses. In this very refractory population, both in large-cell lymphoma and follicular lymphoma, we’re seeing a substantial number of patients [achieving] complete remissions and those remissions are indeed durable. It’ll be interesting to see how these 2 therapies evolve going forward.”

**REFERENCES**

IMPORTANCE SAFETY INFORMATION

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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.

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IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 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 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, 19% 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 lymphocytes 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.
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

INFORMATION [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).

CONTRAINDICATIONS

None.

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 ulceration 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, lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

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

Monitoring and Patient Instruction

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

Adverse reactions [seeWarnings and Precautions (5.1)].

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

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

5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

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

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenia event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 2% to 4% and 15% to 20%, respectively.

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)]. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. 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 (8.1, 8.3)].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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%).
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 (23%), 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>Fatigue*</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.

**Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartateaminotransferase increased</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Albinum decreased</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Alkaline phosphate increased</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
<td>2</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-bmf, 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-bmf 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-bmf. 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.
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.

8.3 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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Treatment Options Continue to Increase in Low-Risk MDS

by KYLE DOHERTY

AZANUCLEOSIDES, SUCH AS AZACITIDINE (Onureg), remain the backbone of disease-modifying therapy for patients with myelodysplastic syndromes (MDS). However, new adjuncts are leading to longer remissions and disease-free survival in patients with low-risk disease, according to Michael R. Savona, MD.

“Lower-risk MDS is a bit of a complicated term to unpack,” said Savona, head of Hematology, Cellular Therapy, and Stem Cell Transplant at Vanderbilt University Medical Center in Nashville, Tennessee, during a presentation during the 39th Annual Chemotherapy Foundation Symposium (CFS®): Innovative Cancer Therapy for Tomorrow®, hosted by Physicians’ Education Resource® (PER®), LLC. “Except for the patients with very low risk, patients less than [age] 60 [years can] expect a median survival of anywhere from 5 to 10 years. For patients over 60 [years], low-risk disease has a mean survival of 5 years or less. It’s important to note that most patients with MDS are older than 60 [years]. The median [age of] diagnosis is between 70 and 73 years.”

THE ROLE OF CLONAL HEMATOPOIESIS
Unexplained cytopenias, such as clonal cytopenias of undetermined significance (CCUS), are an active area of investigation in MDS. Clonal hematopoiesis (CH) refers to the clones present in a significant number of cells, with a variant allele frequency approximately 2% or higher in myeloid mutation-associated genes. CH repeatedly occurs in genes associated with epigenetic function, splicing, and DNA damage repair.²

Most patients with clonal hematopoiesis of indeterminate potential do not develop MDS; however, a significant number of patients develop CCUS and ultimately MDS. One-third of these patients will eventually develop acute myeloid leukemia (AML).³ CCUS is determined if 1 or more somatic mutations associated with myeloid neoplasms are detected in peripheral blood cells or bone marrow with an allele burden of 2% or higher; cytopenia lasts longer than 4 months in 1 or more peripheral blood cell lineages; diagnostic criteria are not met for myeloid neoplasms; and all other causes of cytopenia are excluded.²

“We are looking at new therapies for CCUS, as CCUS is evolving to an interventional state,” Savona explained. “It’s moving very quickly with the discovery in the laboratory of new clinical interventions. We are taking a couple of different approaches to try and slow down the evolution from CCUS to MDS, including targeted therapies and anti-inflammatory approaches.”

Luspatercept-aamt (Reblozyl)—a fusion protein containing a modified activin receptor type IIb that acts as a transforming growth factor-β ligand trap, blocking the inhibitory signals of late-stage erythropoiesis—was approved in 2020 for the treatment of patients with MDS. Specifically, the agent is indicated for the treatment of anemia failing an erythropoiesis-stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low-risk to intermediate-risk MDS with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis.³

The agent acts on late-stage erythropoiesis, ultimately increasing the number of mature red blood cells in circulation. In the phase 3 MEDALIST study (NCT02631070), investigators compared luspatercept with placebo in patients with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis.³

A total of 229 patients were randomized 2:1 to receive either luspatercept or placebo. The median age of the trial population was 71 years (range, 26-95). The median time since original diagnosis of MDS was 41.8 months (range, 3-421) and the median serum erythropoietin level was 153.2 U/L (range, 12-2760).

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“Luspatercept is the hottest ‘new toy’ we have to treat patients with MDS. It’s been very useful in patients with lower risk, and we are still trying to figure out all the different places we can use this therapy in myeloid disease.”

—MICHAEL R. SAVONA, MD

TOP TAKEAWAYS

- The risk of MDS from CCUS is dependent on genotypic characteristics, likely specific variants.
- Luspatercept provides a new therapy specifically to treat anemia in patients with low-risk MDS.
- Oral azacytidine has a role in MDS, but more data are needed to determine what that looks like.

AGENTS LOOKING TO TRANSFORM MDS TREATMENT LANDSCAPE

Luspatercept-aamt (Reblozyl)—a fusion protein containing a modified activin receptor type IIb that acts as a transforming growth factor-β ligand trap, blocking the inhibitory signals of late-stage erythropoiesis—was approved in 2020 for the treatment of patients with MDS. Specifically, the agent is indicated for the treatment of anemia failing an erythropoiesis-stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low-risk to intermediate-risk MDS with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis.³

The agent acts on late-stage erythropoiesis, ultimately increasing the number of mature red blood cells in circulation. In the phase 3 MEDALIST study (NCT02631070), investigators compared luspatercept with placebo in patients with ring sideroblast-positive, low-risk MDS.

A total of 229 patients were randomized 2:1 to receive either luspatercept or placebo. The median age of the trial population was 71 years (range, 26-95). The median time since original diagnosis of MDS was 41.8 months (range, 3-421) and the median serum erythropoietin level was 153.2 U/L (range, 12-2760).
At the prespecified checkpoints (8, 12, and 16 weeks), patients in the luspatercept group (n = 153) had a greater response rate compared with patients receiving placebo (n = 76). At week 8, the overall response rate (ORR) in the luspatercept group was 38% (95% CI, 30%-46%) compared with 13% (95% CI, 6%-23%) in the placebo group. For the totality of the trial (weeks 1-48), the ORR for patients treated with luspatercept was 28% (95% CI, 21%-36%) vs 7% (95% CI, 6%-23%) in the placebo group. For 38% (95% CI, 30%-46%) compared with 13% (95% CI, 8%-23%) in the placebo group.

In terms of safety, luspatercept was found to be very well tolerated. Adverse effects (AEs) of any grade in the luspatercept group included fatigue (27%), diarrhea (22%), and dizziness (20%). Grade 3 AEs were rare and included fatigue (5%) and asthenia (3%).4

“Luspatercept is not clearly disease modifying, but certainly improves anemia and likely quality of life,” Sovona said. “ASTX727 [oral decitabine plus cedazuridine] is a bit of a practical development, but certainly an improvement in quality of life in the disease-modifying area of treatment for MDS.”

ASTX727 is a novel cytidine deaminase (CDA) inhibitor. The administration of oral decitabine with a CDA inhibitor facilitates enhanced bioavailability of decitabine at low doses. ASTX727 has the potential for improved efficacy due to the increased systemic exposure caused by systemic CDA inhibition and more convenient chronic administration.1,5

ASTX727 was evaluated against intravenous (IV) decitabine monotherapy in the phase 3 ASCERTAIN trial (NCT03306264). The trial enrolled 133 patients with intermediate/high-risk MDS, chronic myelomonocytic leukemia, and AML. Patients were randomized 1:1 to sequence A or sequence B. In sequence A, patients received 1 tablet of ASTX727 daily for 5 days in cycle 1, then 1 hour of IV decitabine daily for 5 days in cycle 2, and 1 tablet of ASTX727 daily for 5 days in subsequent cycles. Sequence B followed the same dosing schedule but administered IV decitabine in cycle 1 and ASTX727 in cycle 2.

The median age in the trial population was 71 years (range, 44-88). Most patients (59%) had an ECOG performance score of 1 and were intermediate risk (68%). The study met its primary end point of total 5-day decitabine area under the curve (AUC) equivalence, defined as oral/IV 90% (95% CI, 80%-125%). The oral/IV 5-day decitabine AUC was 98.9% (90% CI, 92.7%-105.6%).5

The ORR in the study was 61.7% (95% CI, 52.8%-69.9%) and 22% of patients achieved a complete response (CR). The median duration of CR was 14.0 months, and the median duration of best response was 12.7 months. At a median follow-up of 32 months, the median overall survival was 31.7 months (95% CI, 28-not estimable).5

“After some experience in mice that we have had some experience in mice that we conducted indicating that cedazuridine is necessary for azacitidine to actually be beneficial if given orally, there is a phase 1 study of ASTX030 [oral azacitidine plus cedazuridine],” Sovona said. “This is a similar combination [to ASTX727].”

ASTX030 was found to be safe and clinically active in patients with AML in a phase 1 dose-finding study (NCT00528983). Patients were treated with 200 or 300 mg of CC-486 daily or twice daily for 14 or 21 days. Investigators noted that extending ASTX030 administration beyond 7 days could lead to an increase in the number of leukemic cells exposed to azacitidine over the course of the cycle and result in improved response.

“[ASTX030] has a place in MDS; we just can’t quite figure out what it is,” Sovona concluded. “Luspatercept is the hottest ‘new toy’ we have to treat patients with MDS. It’s been very useful in patients with lower risk, and we are still trying to figure out all the different places we can use this therapy in myeloid disease.”

REFERENCES
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.
Novel Combination Looks to Capitalize on Synergy of B7-H3/PD-1 Blockade

by BRITTANY LOVELY

EXPRESSION OF B7-H3, a novel molecule of the B7 family, has been associated with undesirable treatment outcomes and has a potential role in the activation and inhibition of immune cell response.1 The investigational monoclonal antibody enoblituzumab has demonstrated activity in preclinical studies and in combination with pembrolizumab (Keytruda) in phase 1/2 studies in patients with checkpoint inhibitor-naïve head and neck squamous cell carcinoma (HNSCC) and non–small cell lung cancer (NSCLC).2

Investigators have demonstrated that more than 50% of patients across tumor types were positive for B7-H3 expression via immunohistochemistry. Specifically, for those with NSCLC (74% positive expression), B7-H3 correlated with ineffective anti–PD-1 therapy, and for those with cutaneous squamous cell carcinoma (85% positive expression), B7-H3 expression was higher in those who were immunocompetent.1

Patients with HNSCC who have relapsed or have metastatic disease have survival outcomes of approximately less than 1 year with the best available therapies.2 Activity has been observed with PD-1 inhibitors; however, investigators are pursuing synergistic pathways which may lead to improved outcomes with combination regimens.

UNPACKING THE ROLE OF ENOBLITUZUMAB

B7-H3, also known as CD276, has limited expression in normal tissue, making it an attractive target for therapeutic development. Enoblituzumab is a fragment crystallizable (Fc) optimized humanized IgG1 monoclonal antibody with an antigen-binding fragment with a high affinity for B7-H3. Further, the Fc structure has a high affinity for activating CD16A and a low affinity for inhibiting CD32B, with the potential enhancement of adaptive immune responses.2

In a phase 1 study (NCT01391143) enoblituzumab had a tolerable safety profile with no drug-related adverse effects (AEs) that led to study discontinuation and no maximum tolerated dose was defined up to 15 mg/kg among patients with B7-H3-expressing cancers. Patients were heavily pretreated with a median of 3 prior lines of therapy (range, 0-7) and experienced disease stabilization over more than 12 weeks; tumor shrinkage ranged from 2% to 69% across tumor types.1

Efficacy data from the phase 1/2 CP-MGA271-03 study (NCT02475213) demonstrated that anti–B7-H3 and anti–PD-1 blockade with enoblituzumab and pembrolizumab nearly doubled overall response rates compared with anti–PD-1 blockade alone in comparator studies. Investigators enrolled patients with HNSCC, NSCLC, melanoma, and urothelial cancer to the study. In terms of safety, 27.1%

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FIGURE. Evaluation of B7-H3–Directed Therapy in HNSCC in CP-MGA271-06 Study2,5

NCT04634825

Eligibility criteria

• Patients ≥ 18 years with histologically proven recurrent or metastatic HNSCC not curable by local therapy
• No prior systemic therapy for HNSCC in the recurrent or metastatic setting
• Patients who completed systemic therapy
> 6 months before the study, if given as part of multimodal treatment for locally advanced disease, are eligible
• Primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx
• ECOG performance status of 0 or 1
• Life expectancy ≥ 6 months
• At least 1 radiographically measurable target lesion per RESIST 1.1
• An identified formalin-fixed, paraffin-embedded tumor specimen for immunohistochemical evaluation of pharmacodynamic markers of interest
• PD-L1 expression level that is either:
  • Positive (CPS ≥ 1) for the retifanlimab cohort
  • Negative (CPS < 1) for the tebotelimab cohort

End points

Primary
• ORR

Select secondary
• PFS
• DCR
• DOR
• OS

CPS, combined positive score; DCR, disease control rate; DOR, duration of response; HNSCC, head and neck squamous cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
Investigators hypothesize that the simultaneous blockade of B7-H3 and PD-1 or B7-H3 and PD-1 and LAG3 may have the potential to sustain the immune activation and antitumor activity that is mediated by enoblituzumab based on in vitro data. Therefore, the proof-of-concept phase 2 trial was initiated to evaluate enoblituzumab in combination with retifanlimab or tebotelimab for the treatment of patients with recurrent or metastatic HNSCC not curable by local therapy with no prior systemic therapy for HNSCC in the recurrent or metastatic setting (FIGURE 2). Retifanlimab is an investigational, humanized, anti-PD-1 monoclonal antibody that binds to PD-1 with affinity 4 times greater than nivolumab (Opdиво) and 6 times greater than pembrolizumab. Tebotelimab is a bispecific DART molecule engineered against PD-1 and LAG3, disrupting the pathways that so that T-cell function may be restored. The agent blocks binding of PD-1 or PD-L1 to PD-1 as well as major histocompatibility complex class II to LAG3. Patients will be assessed for PD-L1 expression and stratified into cohorts based on combined positive score (CPS). Investigators plan to enroll approximately 50 patients with a CPS of 1 or higher to receive enoblituzumab at 15 mg/kg plus retifanlimab at 375 mg every 3 weeks for up to 35 cycles. Safety evaluations for dose-limiting toxicities will be conducted through day 7 of cycle 2 for the first 12 patients.2,5 The primary end point is objective response rate, with secondary end points of progression-free survival, disease control rate, duration of response, and overall survival. Exploratory objectives of the trial include relationships between pharmacokinetics, pharmacodynamics, safety, and antitumor activity; relationships between PD-1, PD-L1, B7-H3, and LAG3 expression on tumor cells and response; and peripheral biomarkers and correlation with potential clinical response.2

Patients whose primary tumor site is the upper esophagus, salivary gland, or nasopharynx of any histology or those with disease suitable for local therapy with curative intent are excluded from enrollment. Further, patients who have received prior therapy with an anti-B7-H3, anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-LAG3 agent are not eligible. The trial is open for enrollment.2

of patients (N = 133) experienced grade 3 or higher AEs, the most common of which were infusion-related reactions (6.8%). An AE of special interest was pneumonitis, which was reported in 3.8% of patients with 2 patients having a grade 3 or higher event; pneumonitis led to death in 1 patient.4 Investigators noted that the AEs were consistent with previously reported data for the single agents.

Patients with HNSCC and NSCLC were stratified by those who received prior anti–PD-1/PD-L1 therapy and those who were treatment naïve. Among 18 treatment-naïve patients with HNSCC and were evaluable for response, 33.3% had a partial response or complete response vs no responses reported for the 19 patients who received prior anti–PD-1/PD-L1 therapy. Stable disease was reported in 27.8% and 47.9% of patients, respectively.

Among responders, 15 had B7-H3 expression of 10% or higher on tumor cells per immunohistochemistry. Among these individuals, 40.0% had a complete or partial response and 73.3% had a complete response, partial response, or stable disease at data cutoff.4 Investigators compared the response rate elicited with the combination in the treatment-naïve cohort with comparator studies and demonstrated that it was nearly double of that in those who received single-agent anti–PD-1 blockade alone (TABLE).4,4 Although the populations in the combination study were smaller, the efficacy data warrant further investigative efforts as a potential strategy to improve tumor responses.

### COMBINATIONS WITH ENOBLITUZUMAB MOVE AHEAD

<table>
<thead>
<tr>
<th>Blockade</th>
<th>Anti–B7-H3 plus anti–PD-1</th>
<th>Anti–PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent(s)</td>
<td>Enoblituzumab plus pembrolizumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Trial name (ClinicalTrials.gov identifier)</td>
<td>CP-MGA271-06 study (NCT04634825)</td>
<td>CheckMate 141 (NCT02105636)</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>240</td>
</tr>
<tr>
<td>ORR</td>
<td>33%</td>
<td>13%</td>
</tr>
</tbody>
</table>

HNSCC, head and neck squamous cell carcinoma; ORR, objective response rate.

**TABLE. Efficacy Data for Anti–B7-H3 plus Anti–PD-1 Blockade vs Anti–PD-1 Blockade in HNSCC**2,4

**REFERENCES**

2. Obara G, Sun J, Luo D, Bohac C. Phase II trial of enoblituzumab plus retifanlimab or tebotelimab for the treatment of patients with recurrent or metastatic HNSCC not curable by local therapy with no prior systemic therapy for HNSCC in the recurrent or metastatic setting (FIGURE 2).5
NOW APPROVED

EXKIVITY™
mobocertinib
40 mg capsules

The first oral therapy for EGFR Exon20 insertion+ mNSCLC patients post platinum-based chemotherapy

INDICATION
EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLONGATION and TORSADES DE POINTES
See full prescribing information for complete boxed warning.
• EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation.
• Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc.
• Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation.

WARNINGS AND PRECAUTIONS

QTc Prolongation and Torsades de Pointes
EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250-patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs), 1.2% of patients had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with baseline QTc greater than 470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation.

Interstitial Lung Disease (ILD)/Pneumonitis
EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population, ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.

Cardiac Toxicity
EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure, which can be fatal. In the pooled EXKIVITY safety population, heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%),...
EXKIVITY did not enroll patients with baseline QTc greater than 1.2%. Of patients had a QTc interval >500 msec and 11% of patients who had scheduled and unscheduled electrocardiograms (ECGs), prolongation, including Torsades de Pointes, which can be fatal. In EXKIVITY can cause life-threatening heart rate–corrected QT (QTc).

WARNINGS AND PRECAUTIONS

IMPORTANT SAFETY INFORMATION (CONT’D)

first-degree ativoventricular block [0.4%], second-degree ativoventricular block [0.4%], left bundle branch block [0.4%], supraventricular extrasystoles [0.4%], and ventricular extrasystoles [0.4%] also occurred in patients receiving EXKIVITY. Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity.

Diarrhea
EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population, diarrhea occurred in 93% of patients, including 26% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days, but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehhydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly. Advise patients to start an anti-diarrheal agent (eg, loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity.

Embry-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY.

ADVERSE REACTIONS
The most common (>20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

DRUG INTERACTIONS

CYP3A Inducers
Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations, which may reduce EXKIVITY antitumor activity. Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

CYP3A Substrates
Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of hormonal contraceptives with EXKIVITY. Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information.

Prolonged QTc Interval
EXKIVITY can cause QTc interval prolongation. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs.

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Females and Males of Reproductive Potential
Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

Lactation
There are no data on the presence of mobocertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-844-217-6668 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of Prescribing Information, including Boxed Warning, on the following pages.

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

EXKIVITY™ (MOBOCERTINIB)

WARNING: QTc Prolongation and Torsades de Pointes

- EXKIVITY can cause life-threatening heart rate–corrected QTc (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation [see Warnings and Precautions (5.1)].
- Avoid use of concomitant drugs which are known to prolong QTc [see Warnings and Precautions (5.1), Drug Interactions (7.1, 7.3)].
- Withhold the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation [see Dosage and Administration (2.3)].

1 INDICATIONS AND USAGE

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.7)], whose disease has progressed or on platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection: Select patients with locally advanced or metastatic NSCLC for treatment with EXKIVITY based on the presence of EGFR exon 20 insertion mutations [see Clinical Studies (14)]. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage: The recommended dosage of EXKIVITY is 160 mg orally once daily until disease progression or unacceptable toxicity.

Take EXKIVITY with or without food [see Clinical Pharmacology (12.3)], at the same time each day. Swallow EXKIVITY capsules whole. Do not open, chew or dissolve the contents of the capsules.

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time.

If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

2.3 Dosage Modifications for Adverse Reactions: EXKIVITY dose reduction levels for adverse reactions are summarized in Table 1.

Table 1: Recommended EXKIVITY Dose Reductions

<table>
<thead>
<tr>
<th>Dose Reductions</th>
<th>Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>120 mg once daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>80 mg once daily</td>
</tr>
</tbody>
</table>

Recommended dosage modifications of EXKIVITY for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc Interval Prolongation and Torsades de Pointes [see Warnings and Precautions (5.1)]</td>
<td>Grade 2 (QTc interval ≥500 msec)</td>
<td>First Occurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withhold EXKIVITY until ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upon recovery, resume EXKIVITY at the same dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withhold EXKIVITY until ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (QTc interval ≥501 msec or QTc interval increase of ≥60 msec from baseline)</td>
<td>First Occurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withhold EXKIVITY until ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)</td>
<td>Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>Intestinal Lung Disease (ILD)/pneumonitis [see Warnings and Precautions (5.2)]</td>
<td>Any grade</td>
<td>Withhold EXKIVITY if ILD/ pneumonitis is suspected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.</td>
</tr>
</tbody>
</table>

2.4 Dosage Modifications for Moderate CYP3A4 Inhibitors: Avoid concomitant use of moderate CYP3A4 inhibitors with EXKIVITY. If concomitant use of a moderate CYP3A4 inhibitor cannot be avoided, reduce the EXKIVITY dose by approximately 50% (i.e., from 160 to 80 mg, 120 to 40 mg, or 80 to 40 mg) and monitor the QTc interval more frequently. After the moderate CYP3A4 inhibitor has been discontinued for 3 to 5 elimination half-lives, resume EXKIVITY at the dose taken prior to initiating the moderate CYP3A4 inhibitor [see Drug Interactions (7.3)].

2.5 Dosage Modifications for Moderate CYP3A Inducers: Avoid coadministration of moderate CYP3A inducers during treatment with EXKIVITY. If coadministration of a moderate CYP3A inducer cannot be avoided, gradually increase the EXKIVITY once-daily dose in 40-mg increments after 7 days of treatment with EXKIVITY and the moderate CYP3A inducer as tolerated, up to a maximum of twice the EXKIVITY dose that was tolerated prior to initiating the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, resume the EXKIVITY dose that was tolerated prior to initiating the moderate CYP3A inducer.

5 WARNINGS AND PRECAUTIONS

5.1 QTc Prolongation and Torsades de Pointes: EXKIVITY can cause life-threatening heart rate–corrected QTc (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250-patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs) (see Adverse Reactions (6.1), Clinical Pharmacology (12.2)), 1.2% of patients had a QTc interval ≥550 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with a baseline QTc greater than 470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY [see Drug Interactions (7.2)], which may further prolong the QTc [see Drug Interactions (7.3)]. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation [see Dosage and Administration (2.3)].

5.2 Intestinal Lung Disease (ILD)/Pneumonitis: EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)], ILD/pneumonitis occurred in 4.3% of patients including 0.9% Grade 3 events and 1.2% fatal events. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed [see Dosage and Administration (2.3)].

5.3 Cardiac Toxicity: EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)], heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure. EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes [see Warnings and Precautions (5.1)].
Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXKIVITY (N = 114)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>92</td>
<td>22</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>46</td>
<td>4.4**</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>2.6**</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39</td>
<td>0.9**</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
<td>4.4**</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>18</td>
<td>1.8**</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY** (N = 114)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased red blood cells</td>
<td>59</td>
<td>3.5</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

Heart failure occurring in 1% of patients receiving EXKIVITY. Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity [see Dosage and Administration (2.3)].
organogenesis resulted in embryolethality (embryo-fetal death) and maternal toxicity at plasma exposures [see Clinical Pharmacology (12.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology (12.1)], EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryolethality (embryo-fetal death) and maternal toxicity at plasma exposures approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose [see Data].

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

Data

Animal Data

In an embryo-fetal development study, once-daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose). Adverse effects on embryo-fetal development at this dose level included embryolethality due to post-implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high-dose level (10 mg/kg).

8.2 Lactation

Risk Summary

There are no data on the presence of mobocertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

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

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective (see Drug Interactions (7.2)).

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 114 patients [see Clinical Studies (14)] who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (89% vs 47%) and serious adverse reactions (64% vs 36%) in patients 65 years and older as compared to those younger than 65 years.

8.6 Renal Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment [see Dosage and Administration (2.4), Warnings and Precautions (5.1)].

8.7 Hepatic Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN]) and aspartate aminotransferase [AST] > ULN or total bilirubin > 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin ≥1.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY has not been established for patients with severe hepatic impairment (total bilirubin ≥3 times ULN and any AST) [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

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

17.1 QTc Interval Prolongation and torsades de Pointes

Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see Warnings and Precautions (5.1)].

17.2 Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain [see Warnings and Precautions (5.2)].

17.3 Cardiac Toxicity

Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see Warnings and Precautions (5.3)].

17.4 Diarrhea

Inform patients that EXKIVITY may cause diarrhea, which may be severe in some cases and should be treated promptly. Advise patients to have anti-diarrheal medicine readily available and promptly start anti-diarrheal treatment (e.g., loperamide), increase oral fluids and electrolyte intake, and contact their healthcare provider if diarrhea occurs [see Warnings and Precautions (5.4)].

17.5 Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5)].

17.6 Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7.2)]. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

17.7 Missed Dose

Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day [see Dosage and Administration (2.2)].
Influx of Therapies in NETs Prompts Questions Over Combinations and Sequencing

by RYAN SCOTT

TYROSINE KINASE INHIBITORS (TKIS), hypoxia-inducible factor 2α (HIF-2α) inhibitors, and peptide receptor radiotherapy are generating excitement in the field of neuroendocrine tumors (NETs), explained Diane Reidy-Lagunes, MD. However, until more definitive data are available regarding the optimal sequence of treatment, recommendations should be based predominantly on the patient, the location of their disease, and their performance status.

“In the past year, the promise of additional therapies and potentially altering therapies in order to maintain quality of life [has been] worked [on] on the investigative side,” Reidy-Lagunes said. “There has not been an FDA-approved drug in the United States [specifically for NETs], although over the past 5 years the landscape has really changed. Therefore there are multiple therapies to consider.”

In an interview with OncologyLive®, Reidy-Lagunes, associate deputy physician in chief of Regional Care Network, physician ambassador for the Patient Family Advisory Council for Quality, and president of Memorial Sloan Kettering Cancer Center medical staff in New York, New York, unpacked recent updates in NETs (TABLE 1-3).

**TABLE. Select Agents Under Investigation for Patients With NETs**

<table>
<thead>
<tr>
<th>Agent (trial; ClinicalTrials.gov identifier)</th>
<th>Pancreatic NETs (n = 55)</th>
<th>GI-NETs (n = 56)</th>
<th>Total population (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib (TALENT; NCT02678780)</td>
<td>ORR: 44.2%</td>
<td>ORR: 16.4%</td>
<td>ORR: 29.9% (95% CI, 21.6%-39.6%)</td>
</tr>
<tr>
<td></td>
<td>Median DOR: 19.9 months (range, 8.4-30.8)</td>
<td>Median DOR: 33.9 months (range, 10.6-38.3)</td>
<td>Median PFS: 15.7 months (95% CI, 14.1-19.5)</td>
</tr>
<tr>
<td>Sunitinib (FIRSTMAPPP; NCT01371201)</td>
<td>12-month PFS rate: 35.9%</td>
<td>12-month PFS rate: 18.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median PFS: 8.9 months (95% CI, 5.5-12.7)</td>
<td>Median PFS: 3.6 months (95% CI, 3.1-6.1)</td>
<td></td>
</tr>
<tr>
<td>Belzutifan (Study 004; NCT03401788)*</td>
<td>ORR: 49% (95% CI, 36%-62%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median DOR: NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DOR ≥ 12 months: 56%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOR, duration of response; GI, gastrointestinal; NETs, neuroendocrine tumors; NR, not reached; ORR, overall response rate; PFS, progression-free survival.

*Agent is approved by the FDA for the treatment of patients with von Hippel-Lindau–associated renal cell carcinoma.

**HOW HAS THE ROLE OF TKIS EVOLVED IN NETS?**

Many therapies are available for [patients with] NETs, including somatostatin analogues, targeted therapies, peptide receptor radiotherapy, and chemotherapy. However, [it’s important to discuss] findings from 2021 that perhaps haven’t reached community oncologists yet.

The role of lenvatinib [Lenvima] in gastrointestinal [GI] NETs is important. Findings from the phase 2 TALENT study [NCT02678780] showed a response rate of 44% in pancreatic NETs and 16% in GI NETs, which is the highest reported response rate in GI cancers.¹

Another important drug is surufatinib, which was evaluated in 2 studies in China [NCT02589821; NCT02588170] and approved in China for patients with pancreatic NETs and extra-pancreatic NETs. The response rates ranged from 10% to 20%. In July 2021, the FDA accepted the filing of a new drug application for surufatinib for patients with pancreatic and extrapancreatic NETs, so we should hear whether that agent is approved for use in the United States soon.

The role of TKIs in NETs is evolving and moving forward, which is exciting. There have been multiple reports that indicated the role of sunitinib [Sutent] could be promising, [including from] a randomized phase 2 study [FIRSTMAPPP; NCT01371201] of sunitinib in pheochromocytoma/paraganglioma. The study met its primary end point; the 12-month progression-free survival [PFS] rate was 36% with sunitinib vs 19% with placebo.²

**Which studies have underscored the importance of personalized treatment in NETs?**

There was an important study on mortality in NETs that was published in the Journal of the National Comprehensive Cancer Network. Investigators looked at a retrospective registry of 8607 patients from Toronto. In patients with small intestine, colon, and rectal NETs, the risk of non-cancer-associated death rates ranged from 10% to 20%.

In July 2021, the FDA accepted the filing of a new drug application for surufatinib for patients with pancreatic and extrapancreatic NETs, so we should hear whether that agent is approved for use in the United States soon.

The role of TKIs in NETs is evolving and moving forward, which is exciting. There have been multiple reports that indicated the role of sunitinib [Sutent] could be promising, [including from] a randomized phase 2 study [FIRSTMAPPP; NCT01371201] of sunitinib in pheochromocytoma/paraganglioma. The study met its primary end point; the 12-month progression-free survival [PFS] rate was 36% with sunitinib vs 19% with placebo.²
outweighed the risk of cancer-specific death. In our patient population, one of the biggest challenges is the heterogeneity of the disease. Some patients can live with the disease and some patients pass because of the disease. Being mindful that not every patient needs aggressive treatment is critical.

In the study [results], investigators noted that [patients with] bronchopulmonary NETs and pancreatic NETs usually succumb to the disease because these tumors tend to have a more aggressive pattern. This study [emphasizes the importance of] knowing your patient. It is possible to wait on [treating] certain patient populations, so that we don’t over treat. Many patients with GI NETs can pass from other non–cancer-related problems, and it is important to be mindful of that.

**Q** What was exciting about the approval of the HIF-2α inhibitor belzutifan (Welireg)?

In August 2021, the FDA approved belzutifan. The drug was approved for patients with germline mutations for von Hippel-Lindau syndrome, which is common in pancreatic NETs. The pivotal phase 1 Study 004 [NCT03401788] enrolled 61 patients with the von Hippel-Lindau germline gene mutation, and the primary end point was objective response rate [ORR]. The ORR was 49% [across all subgroups, and] the duration of response was at least 12 months [in most patients].

**Q** How are you utilizing the peptide receptor radiotherapy lutetium 177 (177Lu) dotatate (Lutathera) in this space? [177Lu dotate] is a game changer for patients. It consists of 4 treatments every 8 weeks and then patients are done, which is nice. My mentor used to tell me grade 1 to 2 nausea every day is probably worse from a patient QOL perspective than grade 3 nausea for 2 days. It is important to be mindful of the adverse effects [AEs] of the different therapies given to patients. Peptide receptor radiotherapy is a nice therapy because the chances of long-term AEs are rare, but serious.

Patients can have lower blood counts and there’s a rare but serious risk of preleukemia and leukemia [with peptide receptor radiotherapy]. In general, those are therapies that are well tolerated. They’re not readily available to everyone. In the community, often you must submit a referral to an academic center to be able to provide that treatment, but more and more providers are able to find an appropriate place to be able to give patients the therapy that is needed.

The role of peptide receptor radiotherapy, which has altered the way that patients are cared for now that it is FDA approved in the United States, is evolving as well. It is important to ask the question: Should we add therapies onto that treatment or should we sequence treatments. The right sequencing of therapies is unknown. Many studies are ongoing now to test the role of combinations with that treatment. At this point, we do not recommend any combination of treatments with 177Lu dotate.

**Q** Without level 1 evidence, how do you approach treatment sequencing?

The biggest challenge, which I’ll address during my talk, is that we don’t know what the optimal sequencing strategy is. What is the best second- and third-line treatment? Often it depends on the patient as well as the location of their disease and their overall performance status.

In a patient with high tumor burden where the goal is tumor shrinkage, you may try a combination of oral cytotoxic therapies, whereas in a patient that has low-volume disease and is asymptomatic, you may be able to just watch for a while. That personalized approach in NETs can be challenging because we don’t have great data to help us drive the different lines of therapies that we have. We don’t have enough of a patient population to be able to do sequencing studies in an accurate and efficient way.

**Q** Could immunotherapy become part of the NET paradigm?

The role of immunotherapy in NETs still is a work in progress. Several trials with well-differentiated NETs failed to meet their primary end point of response. One trial in poorly differentiated carcinomas did show some promise, but unfortunately other studies failed to show that [same promise].

Other studies are trying to manipulate the immune system, but it doesn’t look like NETs are hot tumors, potentially because these are tumors without alterations and without high mutational burden. There are many reasons why the immune system doesn’t recognize the NET as well as it does other tumors. There are some virus-type protocols with immunotherapy that are coming, so there’s more to come. However, in well-differentiated NETs, there is currently no role to use checkpoint blockade.
Saif Shares Insights on Single-Agent PARP Inhibitors and Combination Therapies for Pancreatic Cancer

by MAGGIE TIBBITT

STUDIES EVALUATING PARP INHIBITORS, metabolic agents, and stroma-targeting strategies are contributing to advances in treatment for patients with pancreatic cancer, according to Wasif M. Saif, MD. As strategies veer toward precision medicine approaches, germline genetic testing will be critical, he said.

“Germline testing is extremely important, not only because it tells us which patient has a genetic mutation linked to pancreatic cancer, but also because it advises us to look for other members in the family who may be at a higher risk of developing pancreatic cancer or other tumors, such as breast, ovarian, prostate, or colorectal cancer,” Saif said. “Also, now we know based on the recent data from the POLO study [NCT02184195] that this testing will help us decide what chemotherapy should be used for those patients.”

In an interview with OncLive® in advance of the 39th Annual Chemotherapy Foundation Symposium® (CFS®), Saif, deputy physician in chief at Northwell Health Cancer Institute and a professor at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in New Hyde Park, New York, discussed the evolving role of PARP inhibitors and anticipated trends for research in pancreatic cancer.

Why are PARP inhibitors necessary in the treatment of patients with advanced pancreatic cancer?

Pancreatic cancer accounts for approximately 3% of all cancers in the United States and approximately 7% of all cancer deaths. Despite the low prevalence of the disease relative to other solid tumors, we know that pancreatic cancer is one of the leading causes of cancer-related death in the United States. Pancreatic cancer is highly resistant to chemotherapy as well as radiation therapy. The current standard of care chemotherapeutic regimens, FOLFIRINOX [leucovorin, 5-fluorouracil, irinotecan, oxaliplatin] and gemcitabine plus nab-paclitaxel [Abraxane], provide disease control, but eventually [the] tumor develops chemotherapy resistance.

Tumors that are deficient in DNA damage repair mechanisms, such as [those with] BRCA mutations, respond better to platinum-based chemotherapy. However, these tumor cells can utilize the PARP [protein] as a salvage DNA repair pathway to prolong survival. Hence, in the presence of a BRCA mutation, the inhibition of the PARP pathway can lead to tumor cell death. This provides a rationale for the use of PARP inhibitors in patients with BRCA-mutated pancreatic cancer.

Which agents have generated the most interest?

Of interest is olaparib [Lynparza], which [was approved by the] FDA based on the results of the phase 3 POLO study [NCT02184195]. The study results showed a doubling of progression-free survival with olaparib compared with placebo as maintenance therapy following frontline platinum-based chemotherapy in patients with advanced BRCA-mutant pancreatic cancer. Other PARP inhibitors include veliparib and rucaparib [Rubraca], which are being tested in pancreatic cancer both as single agents as well as in combination with systemic chemotherapy.

Other important DNA-affecting targets include ATM as well as CLB2 and CHEK2.

Why is it important to understand a patient’s genetic profile before initiating treatment?

It is now recommended by the National Comprehensive Cancer Network [NCCN] that we should be testing all patients who [receive a diagnosis of] pancreatic cancer for germline mutations. The NCCN has also suggested that patients who have somatic mutations can benefit from these targeted agents.

Germline mutations occur in the gametes and can be passed down to offspring, which means that every cell in the entire organism will be affected. On the other hand, somatic mutations occur in a single body cell and cannot be inherited; only tissues derived from that mutated cell are affected. It’s very important that patients should be tested for these genes.

Germline mutation testing must include BRCA1 and BRCA2, [and providers should also consider testing for] microsatellite instability, ATM, and PALB2. It is extremely important that we don’t forget about testing the tumor. It’s not only [important] that we learn about the disease and the stage, but it’s also important that we know about the molecular or the genetic makeup of the tumor. That should be part of the initial work-up [and] will really guide treatment of the patient.

The phase 3 Avenger 500 trial (NCT03504423) investigated the antimitochondrial agent devimistat (CPI-613). How could this agent potentially be used?

Devimistat is a novel lipoate analog that inhibits the TCA [tricarboxylic acid] cycle. It inhibits the dehydrogenase enzyme α-ketoglutarate dehydrogenase complexes. The benefit is that by [targeting these complexes], [the agent] inhibits the entry of glucose- and glutamine-derived carbon, respectively. Pancreatic cancer is dependent on mitochondrial function for enhanced survival and aggressiveness.

A phase 1 study [NCT01835041] cited in Nature evaluated the combination of modified FOLFIRINOX and devimistat, [and] the results showed a very high response rate of 61% with a complete response rate of 17%. Now the randomized phase 3 Avenger 500 study is looking at devimistat in...
Learn about the second indication for ENHERTU and how it may help certain patients with unmet needs

Speaker Information:

Ronan J. Kelly, MD, MBA
Moderator
Director of Oncology at the Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, Texas

Yelena Janjigian, MD
Speaker
Associate Professor and Chief of Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, New York

John L. Marshall, MD
Speaker
GI Oncologist, Washington, DC

ON-DEMAND BROADCAST

Important Safety Information (cont.)

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY
- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Contraindications
None.

Warnings and Precautions
Interstitial Lung Disease / Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

Please see Important Safety Information continued on the next page, and Brief Summary of Prescribing Information, including Boxed WARNINGS on the following pages.
Adverse Reactions

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/ paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in ≥2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch. Please see Brief Summary of Prescribing Information on the next pages.
ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use
Initial U.S. Approval: 2019

BRIEF SUMMARY: See package insert for full prescribing information.

WARNING: INTERSTITIAL LUNG DISEASE AND EMBRYO-FETAL TOXICITY
- Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms [see Dosage and Administration (2.3) in the full prescribing information, Warnings and Precautions (5.1)].
- Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception [see Warnings and Precautions (5.4), Use in Specific Populations (8.1), Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information].

1 INDICATIONS AND USAGE
1.1 Metastatic Breast Cancer
ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14.1) in the full prescribing information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Locally Advanced or Metastatic Gastric Cancer
ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU [see Adverse Reactions (6.1)]. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery [see Dosage and Administration (2.3) in the full prescribing information]. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD [see Dosage and Administration (2.3) in the full prescribing information].

Metastatic Breast Cancer.
In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Locally Advanced or Metastatic Gastric Cancer
In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see Dosage and Administration (2.3) in the full prescribing information].

5.2 Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction [see Dosage and Administration (2.3) in the full prescribing information].

Metastatic Breast Cancer.
In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 62% of patients. Sixteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 23 days (range: 6 to 547). Febrile neutropenia was reported in 1.7% of patients.

Locally Advanced or Metastatic Gastric Cancer
In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

5.3 Left Ventricular Dysfunction
Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Interstitial Lung Disease/Pneumonitis [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Left Ventricular Dysfunction [see Warnings and Precautions (5.3)]

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

Metastatic Breast Cancer.
The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900) [see Clinical Studies (14.1) in the full prescribing information]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

In the pooled 234 patients, the median age was 56 years (range: 28-96), 74% of patients were ≤65 years, 96.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an ECOG performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases. Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in ≥1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.8%), and the following events occurred in one patient each (2.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia. The most common (>20%) adverse reactions, including laboratory abnormalities, were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, diarrhea, hypokalemia, and cough.

Tables 4 and 6 summarize adverse reactions and laboratory abnormalities observed during or 14 days after the last dose of ENHERTU for at least 4 months after the last dose of ENHERTU [see Use in Specific Populations (8.1, 8.3)].
Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients.

### Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study D8301-A-J101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENHERTU 5.4 mg/kg N=234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>79</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29</td>
</tr>
<tr>
<td>Abdominal paina</td>
<td>19</td>
</tr>
<tr>
<td>Stomatitisb</td>
<td>14</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>59</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>46</td>
</tr>
<tr>
<td>Rashia</td>
<td>10</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Anemiac</td>
<td>31</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13</td>
</tr>
<tr>
<td>Interstitial lung diseaseb</td>
<td>9</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headacheb</td>
<td>19</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
</tr>
<tr>
<td><strong>Infections and Infestation</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>15</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>11</td>
</tr>
</tbody>
</table>

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities. Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

### Table 4: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades %</th>
<th>Grades 3 or 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
<td>3.4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>41</td>
<td>0.9</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>38</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 5: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENHERTU 6.4 mg/kg N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3 or 4</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63</td>
<td>4.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>2.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal paina</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Stomatitisb</td>
<td>11</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>Dehydration</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemiaa</td>
<td>58</td>
<td>38</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.6%)
- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)

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**Locally Advanced or Metastatic Gastric Cancer**

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 [see Clinical Studies (14.2) in the full prescribing information]. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in ≥2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestasis, jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (≥2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (≥2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased, white blood cell decreased, neutrophil count decreased, lymphocyte count decreased, platelet count decreased, nausea, decreased appetite, anemia, aspartate aminotransferase increased, fatigued, blood alkaline phosphatase increased, alanine aminotransferase increased, diarrhea, hypokalemia, vomiting, constipation, blood bilirubin increased, pyrexia, and alopecia.

Tables 5 and 6 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.
Events were graded using NCI CTCAE version 4.03. N = number of patients exposed; PT = preferred term.

Table 5: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue$^a$</td>
<td>55</td>
<td>9</td>
<td>44</td>
<td>4.8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>22</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease$^b$</td>
<td>10</td>
<td>2.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>8</td>
<td>3.2</td>
<td>1.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- Cardiac Disorders: asymptomatic left ventricular ejection fraction decrease (8%) [see Warnings and Precautions (5.3)]
- Infections and Infestations: pneumonia (6%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (1.6%)

Table 6: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 6.4 mg/kg N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>74</td>
<td>29</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>58</td>
<td>9</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>30</td>
<td>4.8</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

Other relevant abnormalities were:
- Anemia: decreased
- Total bilirubin increased

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the 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, comparisons of the incidence of antibodies to ENHERTU in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Treatment-induced anti-fam-trastuzumab deruxtecan-nxki antibodies (ADA) developed in 1.7% (14/807) patients who received ENHERTU across all doses. Due to the limited number of patients who tested positive for ADA, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety. In addition, neutralizing activity of anti-ENHERTU antibodies has not been assessed.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (see Data). Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (12.1) in the full prescribing information]. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU (see Clinical Considerations).

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

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data
Human Data
There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data
There were no animal reproductive or developmental toxicity studies conducted with fam-trastuzumab deruxtecan-nxki.

8.2 Lactation
Risk Summary
There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception
Females
ENHERTU 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 ENHERTU and for at least 7 months following the last dose [see Nonclinical Toxicology (13.1) in the full prescribing information].

Infertility
Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility [see Nonclinical Toxicology (12.1) in the full prescribing information].

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

8.5 Geriatric Use
Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger
patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (53%) as compared to younger patients (42%).

Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

8.6 Renal Impairment
No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance [CrCl] ≥60 and <90 mL/min) or moderate (CrCl ≥30 and <60 mL/min) renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]. No data are available in patients with severe renal impairment.

8.7 Hepatic Impairment
No dose adjustment of ENHERTU is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see Dosage and Administration (2.3) in the full prescribing information]. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

17 PATIENT COUNSELING INFORMATION

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

Interstitial Lung Disease
- Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see Warnings and Precautions (5.1)].

Neutropenia
- Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider if they develop a fever, particularly in association with any signs of infection [see Warnings and Precautions (5.2)].

Left Ventricular Dysfunction
- Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity
- Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (6.1)].
- Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months after the last dose [see Use in Specific Populations (8.3)].
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose [see Use in Specific Populations (8.3)].

Lactation
- Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see Use in Specific Populations (8.2)].

Infertility
- Advise males of reproductive potential that ENHERTU may impair fertility [see Use in Specific Populations (8.3)].
combination with modified FOLFIRINOX vs FOLFIRINOX alone for patients with untreated metastatic pancreatic cancer.

This study is important because we know the fibrotic microenvironment may have an advantage in causing resistance to chemotherapy, but we also know that it triggers a lot of metabolic hindrances and constraints on the tumor. A lot of studies have indicated that autophagy is essential in the tumor cell as well as in supporting the stroma, which is consistent with metabolic stress.

We believe that devimistat will enrich the TCA cycle and may be particularly effective against tumors that have baseline metabolic stress, such as pancreatic cancer. I hope that Avenger 500 will provide important data on the validity of this approach and further our understanding of the role of mitochondrial metabolism in therapy response in the first-line treatment of patients with metastatic pancreatic cancer.

What other areas are under investigation?

We are still trying to figure out sequential therapy. We’re trying to [better understand] what regimen [should] be used [in the] first-line [setting], [although] BRCA1 [mutation can guide our choice]. We’re also learning about GATA6, which is a transcription factor, and is based on a special subclassification of pancreatic cancer [that is] based on the Bailey, Collisson, or Moffitt classification.

We believe that certain subtypes of pancreatic cancer lack or are deficient in the GATA6 transcription factor, and we believe that those cell lines are resistant to FOLFIRINOX, which [currently] is the most aggressive [and] more successful regimen. There will be studies looking at those precision oncology approaches [and] sequential therapy. We are trying to [bring regimens used in] the metastatic [setting] to earlier stages of pancreatic cancer.

We are still learning about the pharmacogenetics and metabolic markers of chemotherapeutic agents, and we’ll be looking at pharmacokinetics and other pharmacodynamics. We’re still struggling with the stromal targeting agents.

The HALO-301 study [NCT02715804] looked at combinations with chemotherapy, but we [still] need to learn [more about these agents].

Inflammatory response is very important, and JAK1 and JAK2 inhibitors have been tested in pancreatic cancer in a phase 1/2 study [NCT01858883]. Even though the study did not meet the end point, it did give us some answers, particularly regarding cachexia, which is a huge challenge in pancreatic cancer. Multiple pathways are being investigated at this time, and I believe [that research] will continue.

There is rekindling interest in immunotherapy. Immunotherapy has not been very successful in pancreatic cancer, but we are learning more about it. From experience, [there is] a strong rationale to combine PARP inhibitors with immunotherapy. One of the theories...is that PARP inhibitor-mediated DNA damage can really enhance the recruitment of T cells, which can lead to an upregulation of PD-L1 and [create] a good environment to be attacked with a checkpoint inhibitor. Clinical trials are looking at these things.

Now we are in the stage where

"It is extremely important that we don’t forget about testing the tumor. It’s not only [important] that we learn about the disease and the stage, but it’s also important that we know about the molecular or the genetic makeup of the tumor. That should be part of the initial work-up [and] will really guide treatment of the patient.”

What else are you looking forward in this space?

[First is] the resistance to PARP inhibitors, and [in particular] the ATR/CHK1 pathway. We always say that there is a lifespan to everything. Similarly, when we give a drug to a patient, either an antibody or chemotherapy, [we know the patient will] develop resistance.

If you could relay 1 thing to your colleagues in the community setting, what would it be?

The key take-home message is to know the patient, know the tumor, and know the cancer drug. You need to know the tumor stage and genetics because that’s how you are going to define the first-line therapy and think about maintenance therapy or a clinical trial. [You also have] to know the patient and what they are willing to accept. What are the patient’s characteristics, comorbid conditions, and acceptance about chemotherapy adverse effects?

That is really an important part [of the process]. Make sure the patient understands what you’re talking about and [that] you understand what the patient is asking for.
Personalized Medicine Could Be Key to Bridging Health Disparities in Cancer Care

by JESSICA HERGERT

EXPANDING THE DEFINITION OF personalized medicine to include social determinants of health disparities is needed to ensure patients with cancer receive optimal care, according to Karen Winkfield, MD, PhD. She added that lessons learned from the COVID-19 pandemic have sparked a new wave of enthusiasm to advocate for change and bridge existing gaps in oncology.

“Unfortunately, the COVID-19 pandemic has shown that in the United States, we don’t quite have the public health infrastructure that we need. Not yet,” she said. Winkfield is executive director of the Meharry-Vanderbilt Alliance, the Ingram Professor of Cancer Research, and professor of radiation oncology at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Wakefield delivered these remarks during the Greenspan Lecture at the 39th Annual Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow®, hosted by Physicians’ Education Resource®, LLC (PER®).1

“We have an opportunity to think about [health equity] in a way that impacts communities at large and, more specifically, the individual patients that are walking through our doors. What ways can we [affect] what is happening to the people that we serve?” Winkfield asked during her presentation titled “Precision Medicine: Ensuring Every Patient Gets the Right Treatment at the Right Time.”

PRECISION VS PERSONALIZED MEDICINE

The field of precision oncology has grown significantly in recent years with the integration of broad molecular testing, identification of new prognostic markers, and understanding of mechanisms of resistance. With the development of targeted therapy, many patient populations can receive care that directly reflects unique characteristics of tumor genomics and personal genetics.

However, Winkfield advises health professionals in the field to further broaden the role of precision medicine to include not only genomic factors, but also microbiome features, patient exposures and behaviors, clinical tests, and patient-contributed data to create a knowledge network that will allow for precision medicine to become more personalized.

“There are components of both [precision and personalized medicine] that we really need to think about today as we are talking about all the innovations that are being made in terms of how we manage chemotherapeutics,” Winkfield said. “It is important to think about what we mean when we talk about precision oncology. Are we doing our best to personalize medicine?”

FACTORS OF HEALTH DISPARITIES IN CANCER CARE

Despite the downward trends in cancer-related deaths observed across all racial and ethnic patient populations, health disparities still exist, Winkfield explained. For example, one of the most widely known disparities in cancer care exists between White and African American patients.2

Disparity in overall cancer death between African American and White patients declined from 33% in 1990 to 14% in 2016.2 Achieving health equity remains a key goal in cancer care, Winkfield said.

Although biologic determinants such as genetics, biology, and comorbidities inevitably have a role in contributing to these disparities, Winkfield hypothesized that social determinants, such as socioeconomic status, access to care, and sociocultural barriers, are the main contributors to these gaps.

Social determinants of health include economic stability, neighborhood and physical environment, education, food, community and social context, and health care system factors. Negative social determinants, such as low income; lack of access to transportation, food, and social support; literacy challenges; and limited health care provider availability, are associated with poor health outcomes, including increased mortality and morbidity, lowered life expectancy, increased health care expenditures, decreased health status, and functional limitations.

“The social determinants go beyond just food; it is transportation, employment, literacy, and health literacy. These are all issues we have to think about when we ask ourselves how we design personalized medicine programs and holistic care to the person who is right in front of us,” Winkfield said.

LESSONS LEARNED FROM COVID-19 PANDEMIC

Although social determinants of health are becoming better understood, significant efforts from a socioeconomic and political context are needed to address them and provide precision medicine to all patients.

Notably, the COVID-19 pandemic required rapid integration of many technologies that may start to bridge some of these gaps that are influenced by social determinants of health, such as accessibility. The utility of telemedicine during the height of the pandemic is one lesson that can be taken away. Winkfield underscored that the pandemic showed feasibility with localized or virtual care for certain procedures and patient conversations. Additionally, even without the context of COVID-19, clinical trial consent forms are likely able to be signed virtually rather than having patients come into the clinic.

Importantly, adding virtual elements to cancer care can significantly lower the burden of treatment for patients, particularly for those who live in rural communities or who must rely on public transportation.
“Our ability to innovate the way that we have done with COVID-19—where telehealth is being compensated—these are the sorts of things we need to advocate for because, frankly, it makes it much easier for patients. This is what patient-centric care is about,” Winkfield said.

A study published in the *International Journal of Radiation Oncology, Biology, Physics* stated that achieving health equity is of critical importance for patients receiving radiation therapy and that the renewed passion to protect vulnerable patients observed during the COVID-19 pandemic should continue to address the disparities in care. ³

Winkfield advised oncologists to be advocates of bringing more equitable cancer care in clinical trials and policy implications to their institutions and communities. Additionally developing a diverse workforce and working in direct collaboration with community-engaged researchers are a great start at addressing these gaps.

Specifically, Winkfield called attention to the need for redesigned and inclusive clinical trials. She highlighted the example of multiple myeloma: Although African Americans comprise 20% of the multiple myeloma population in the United States, they comprise only 5% of FDA registration trials in multiple myeloma. ⁵

In addition to African American patients, adolescent/young adults, older adults, other racial/ethnic minorities, LGBTQ+ individuals, individuals in rural areas, and patients of lower socioeconomic status are some of the patients at greatest risk for exclusion from clinical trials.

“If we are only getting the clinical trials in the spaces at the places that are very homogenous or have not done a good job at being inclusive, are we really moving the needle?” Winkfield asked.

Wakefield noted that developing an actionable framework for stakeholders to address cancer care disparities within medically underserved populations is of paramount importance to ensure population-health care is implemented. Wakefield et al. published results of an environmental scan that identified 84 experts across 8 stakeholder groups and 44 patient organizations, 33 of whom participated in a roundtable during which they identified access and treatment barriers or gaps within the cancer care continuum.

The framework developed from these discussions is intended to guide investigators and health care leaders to address and promote health equity in cancer care. ⁵

In addition to health equity, some of these issues include quality of care, communications, and decision-making. Ultimately, developing an understanding of the cross-cutting issues that span the entire cancer care continuum from prevention to detection, diagnosis, and treatment to survivorship and end of life is critical. ⁵

The framework emphasizes the role of patient navigators and their ability to play a supportive role across 4 domains of care: screening to diagnosis, diagnosis to treatment, treatment to survivorship, and across the entire continuum of care. Overcoming the common barriers to care across screening, diagnosis, and treatment will also rely on documentation of efforts made by practices. These data will valuable insight into response to real-world populations access and respond to therapies.

“We need to figure out how we can create an environment where we provide precision oncology, but we provide it for every patient so that every patient gets the right treatment at the right time,” Winkfield concluded.

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**TABLE. Actionable Recommendations for Health Care System Change Across Domains⁵**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Screening</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Survivorship</th>
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<tbody>
<tr>
<td>Develop clear transitions of care processes with accountability and documentation of data requirements</td>
<td>✓</td>
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<td>Document problems with or develop broad-based sustainable solutions for unconscious bias</td>
<td>✓</td>
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<td>Evaluate and adopt best practices from other fields including hiring and recruiting a diverse workforce</td>
<td>✓</td>
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<tr>
<td>Develop health equity scorecard for health systems</td>
<td>✓</td>
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<tr>
<td>Train and educate staff on the use of and access to patient education resources and optimal timing for discussion</td>
<td>✓</td>
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<tr>
<td>Develop and implement a cancer health equity audit and scorecard in geographic locations with large medically underserved populations</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Begin assessment of social determinants of health and other potential barriers prior to first appointment</td>
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<td>Implement strategies for delivering patient-centric clinical trials that facilitate inclusion of representative patients</td>
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<td>Implement multiple cancer research opportunities in the community</td>
<td>✓</td>
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<td>Develop a system-wide campaign to promote research participation</td>
<td>✓</td>
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<tr>
<td>Build infrastructure to capture patient opt-in approaches, demographics, and findings</td>
<td>✓</td>
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<tr>
<td>Set up information technology infrastructure that yields trusted communication channels before, during, and after research for all parties</td>
<td>✓</td>
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<tr>
<td>Replicate the CDC’s National Breast and Cervical Cancer Early Detection Program model for pass-through access for all high-prevalence cancers</td>
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<tr>
<td>Allow patient or caregiver to log in and see provider notes</td>
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<tr>
<td>Implement a survivorship care plan and train primary care providers in survivorship</td>
<td>✓</td>
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<tr>
<td>Involve primary care providers in decision-making process with the patient</td>
<td>✓</td>
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Note: For a full list of references, see the article at OncLive.com.
DATA QUALITY IS ESSENTIAL to improving the United States health care system. But what is data quality? Basically, it is about extracting value for patients, clinicians, and payers. High-quality data are both usable and actionable, whereas low-quality data, such as duplicate records, missing patient names, or obsolete information, create barriers to care delivery and billing/payment issues. These inefficiencies result in monetary losses across the health care system.

Unfortunately, health care has lagged virtually every other industry in leveraging data for strategic and operational advantage. This is not for lack of data—more patient health data are being captured today by medical equipment, digital devices, and apps than ever before. If data are gold, the health care industry is sitting on top of a gold mine.

In general, the industry has done a poor job of mining and refining this gold ore of data to the point of being useful. This is a wasted opportunity because quality data would provide value to all health care stakeholders, including hospitals, payers, health information exchanges, laboratories, and patients.

Effect on Research, Patient Outcomes

Poor data quality have negative ramifications throughout health care. The way we bring new medications to market is a great case in point. The first phase is identifying and developing the medication, a process that comprises less than 20% of the cost of drug development. Next comes clinical trials, which account for most drug development costs.

Clinical trials are long and arduous. Worse, from a data quality standpoint, data still are collected on paper, transferred to computer, and typically not associated with other data sets for similar types of patients or even other patients in that clinical trial. If all this information was easily available and automated, clinical trials would cost less than 10% of what they do now.

In clinical practice, there is a significant lack of aggregated data for patients, leaving clinicians knowing only part of a patient’s story. Further, when a physician sees a patient at the hospital, they need the patient’s ambulatory outpatient records to make sound, evidence-based decisions about appropriate treatment. In far too many cases, however, the data that would inform clinicians at the point of care are trapped in silos scattered across the health care landscape.

Health care has not availed itself of advanced digital technologies such as artificial intelligence (AI) and machine learning, which are being used to transform many other industries. This is in large part because these tools are either not accessible or the quality of health data is so poor that intelligent machines would struggle to process and analyze it for actionable insights into patient care.

In contrast, access to quality health care data would create scenarios in which AI and machine learning can quickly provide clinicians with information at the point of care that enables them to educate patients about their specific condition, offer referrals to appropriate specialists, suggest new medications, and improve outcomes. With the right data and insights, clinicians may be able to match the patient with a clinical trial that could save the patient’s life.

Low-quality data are also a problem for payers because they need data to make decisions, regardless of the condition. Data collection starts when a patient receives a diagnosis, yet the payer may not be aware of it for weeks. So, for example, a patient who receives a diagnosis of cancer may suddenly have to find a specialist and determine whether the practice takes their insurance.

However, if a payer finds out right away that this patient has cancer, the payer can help guide the patient to the right provider, alleviating some of the burden of financial concerns related to medical treatment.

Improving Quality Data

There are 3 main steps to achieving high-quality data. The first is ensuring access to the data the clinician needs. There are still many legacy systems in health care, which house most medical records on an organization’s servers and not on a cloud platform, where they could be more easily accessed and aggregated by authorized users.

Although interoperability and data sharing have improved in the health care setting in recent years, integrations are being built one at a time. Bringing data into a central database—where that information can be turned into gold—remains a challenge.

The next step involves identity management. Much of the value in health data comes from the ability to document longitudinal change in individual patients. Clinicians may, for example, want to see how medications affect lab results for a particular patient. Even if they could connect disparate data sources and have the data funnel into a single database, they cannot associate the data with a specific patient. With effective identity management, it is possible to create a longitudinal patient record that can bring huge clinical and efficiency benefits.

The third phase of improving data quality is to make the data usable or actionable. Once the longitudinal record of accurate patient data is created, it must be organized and easy for clinicians to locate and read. This requires a process called data normalization. Health data can come from multiple sources (ie, electronic health records, laboratories, pharmacy systems, etc), all of which may use different coding for a medical procedure, different terms for a certain test, or even different language to categorize genders.

Data normalization creates a common terminology that enables the semantic interoperability necessary to make data actionable.

There’s no magic bullet for improving health care data quality. It will require a joint effort and the innovation inherent in the free market. There will be companies that help us collect and connect to data, and there will be companies and entities that help us connect to data. There will be technologies that identify the data and others that will normalize the data, and there will be companies that provide quality databases that health care stakeholders can use to perform advanced analytics. The end result will be a health care system that provides better care at a lower cost.

Oleg Bess, MD, is CEO and cofounder of 4medica, which provides clinical data management and health care interoperability software and services.
SET OUT TOWARDS A FUTURE
THE ONLY APPROVED DUAL I-O MAY DELIVER1*

OPDIVO® + YERVOY®
For PD-L1 ≥1% mNSCLC patients, across histology without EGFR or ALK mutations
OPDIVO, in combination with YERVOY, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 ≥1% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
Primary analysis (PD-L1 ≥1%): median OS was 17.1 months (95% CI: 15.0–20.1) with OPDIVO + YERVOY vs 14.9 months (95% CI: 12.7–16.7) with chemo (HR=0.79; 95% CI: 0.67–0.94; P=0.0066).1

OPDIVO + YERVOY with limited chemo
For r/m NSCLC patients, regardless of PD-L1 expression and histology
OPDIVO, in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.
Primary analysis: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY and chemo vs 10.7 months (95% CI: 9.5–12.5) with chemo (HR=0.69; 95% CI: 0.55–0.87; P=0.0006).1

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous use.1,2

Study design: Checkmate 227 was a randomized, open-label phase 3 trial in patients with metastatic or recurrent NSCLC. Key eligibility criteria included patients 18 years or older, stage IV or recurrent NSCLC, ECOG PS 0/1, and no prior systemic anticancer therapy. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. In Part 1a (n=793), patients with PD-L1 ≥1% were randomized to either OPDIVO 3 mg/kg q2w + YERVOY 1 mg/kg q6w (n=396) or platinum-doublet chemotherapy† (n=397). The primary endpoint in Part 1a was OS in patients with PD-L1 ≥1%.

SELECT IMPORTANT SAFETY INFORMATION
Summary of Warnings and Precautions
• OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Severe and Fatal Immune-Mediated Adverse Reactions
• Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
**OPDIVO + YERVOY EFFICACY: OS**

**Checkmate 227:** In a cross-histology trial for patients with mNSCLC (PD-L1 ≥1%)

**Durable survival with OPDIVO + YERVOY: 29% of patients alive at 4 years**

**OS for PD-L1 ≥1% (extended follow-up analysis)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at risk</th>
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<tbody>
<tr>
<td></td>
<td>OPDIVO + YERVOY</td>
</tr>
<tr>
<td>6</td>
<td>295</td>
</tr>
<tr>
<td>12</td>
<td>244</td>
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<td>66</td>
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</table>

- Median PFS with a median follow-up of 54.8 months was 5.1 months (95% CI: 4.1–6.3) with OPDIVO + YERVOY and 5.6 months (95% CI: 4.6–5.8) with chemo alone; HR=0.81; 95% CI: 0.68–0.96.
- 29% of patients enrolled had SQ disease; 71% had NSQ disease.

**mDOR was 23.2 months among OPDIVO + YERVOY responders**

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**
- In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure.

**Common Adverse Reactions**
- In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%).

Please see additional Important Safety Information for OPDIVO and YERVOY throughout and accompanying brief summary of US Full Prescribing Information for OPDIVO and YERVOY on the following pages.
**Checkmate 9LA**: For r/m NSCLC patients, regardless of PD-L1 expression and histology

**Durable survival** with **OPDIVO® (nivolumab) + YERVOY® (ipilimumab) with limited chemo** vs chemo: 38% of ITT patients alive at 2 years\(^1,7\)

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**Overall survival (ITT)**\(^1,7\)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at risk</th>
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<tbody>
<tr>
<td></td>
<td>OPDIVO + YERVOY + chemo (=361)</td>
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<td>39</td>
<td>23</td>
</tr>
</tbody>
</table>

Minimum follow-up of 24.4 months.\(^7\)

- Efficacy results from the pre-specified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) with an 8.1-month minimum follow-up.\(^8\)
- Median PFS at the 23.3-month minimum follow-up: 6.7 months (95% CI: 5.6–7.8) with OPDIVO + YERVOY with chemo and 5.3 months (95% CI: 4.4–5.6) with chemo alone; HR=0.67 (95% CI: 0.56–0.79).\(^7\)
- ORR at the 6.5-month minimum follow-up: 38% (95% CI: 33–43) with OPDIVO + YERVOY with chemo and 25% (95% CI: 21–30) with chemo.\(^8\)
- Median OS at the 24.4-month follow-up analysis: 15.8 months (95% CI: 13.9–19.7) with OPDIVO + YERVOY with chemo and 11.0 months (95% CI: 9.5–12.7) with chemo; HR=0.72 (95% CI: 0.61–0.86).\(^7\)
- 32% of patients enrolled had SQ disease; 68% had NSQ disease.\(^7\)

**Study design**: Checkmate 9LA was a randomized (1:1), open-label phase 3 study of OPDIVO 360 mg q3w in combination with YERVOY 1 mg/kg q6w and 2 cycles of histology-based chemotherapy\(^*\) versus 4 cycles of platinum-doublet chemotherapy\(^*\) as a first-line treatment in patients with metastatic or recurrent NSCLC, regardless of histology or PD-L1 status. Key eligibility criteria included patients 18 years or older, stage IV or recurrent NSCLC, ECOG PS 0/1 and no prior systemic anticancer therapy. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Patients were stratified by histology (SQ vs NSQ), PD-L1 (<1% vs ≥1%), and sex. The primary endpoint was OS. Additional efficacy outcome measures were PFS, ORR, and DOR.\(^1\)

\(^*\)Two cycles of platinum-doublet chemo.\(^1\)

\(^1\)In the intent-to-treat population vs chemo. In Checkmate 9LA, patients received 2 cycles of platinum-doublet chemo q3w in the experimental arm, and 4 cycles in the comparator arm; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in comparator arm only); SQ: paclitaxel + carboplatin.\(^1\)

\(^1\)In Checkmate 9LA, patients in the comparator arm received 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin (optional pemetrexed maintenance therapy in the comparator arm only); SQ: paclitaxel + carboplatin.\(^1\)

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**

- In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

**Common Adverse Reactions**

- In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).
Consistent OS benefit across PD-L1 expression at 2 years\(^7,8\)

**SELECT IMPORTANT SAFETY INFORMATION**

**Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)**

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to improve safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Please see additional Important Safety Information for OPDIVO and YERVOY throughout and accompanying brief summary of US Full Prescribing Information for OPDIVO and YERVOY on the following pages.
Nivolumab (OPDIVO®) + ipilimumab (YERVOY®)–based combinations: National Comprehensive Cancer Network® (NCCN®) recommendations ⁹

Nivolumab (OPDIVO) + ipilimumab (YERVOY) and nivolumab (OPDIVO) + ipilimumab (YERVOY) + platinum-doublet chemotherapy* are recommended as first-line options in metastatic non-small cell lung cancer⁹

NCCN CATEGORY
Useful in certain circumstances

NCCN CATEGORY
Other recommended

- Nivolumab (OPDIVO) + ipilimumab (YERVOY) is recommended as a Category 1, useful in certain circumstances, first-line therapy option for eligible patients with metastatic NSCLC with PD-L1 ≥1% and performance status 0–2 (V5.2021), in tumors that are EGFR, ALK, ROS1, BRAF V600E, NTRK1/2/3, METex14, and RET negative, and no contraindications to PD-1 or PD-L1 inhibitors⁹

- Nivolumab (OPDIVO) + ipilimumab (YERVOY) + platinum-doublet chemotherapy* is recommended as a Category 1, other recommended first-line therapy option for eligible patients with metastatic NSCLC regardless of PD-L1 expression and performance status 0–1 (PD-L1 <1%) or 0–2 (PD-L1 ≥1%) (V5.2021), in tumors that are EGFR, ALK, ROS1, BRAF V600E, NTRK1/2/3, METex14, and RET negative, and no contraindications to PD-1 or PD-L1 inhibitors⁹

Please see updated NCCN Guidelines® for a complete listing of all NCCN-recommended agents, including preferred options. 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.

**SELECT IMPORTANT SAFETY INFORMATION**

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-Mediated Pneumonitis
- OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%). Four patients (0.7%) died due to pneumonitis.

Immune-Mediated Colitis
- OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis and Hepatotoxicity
- OPDIVO and YERVOY can cause immune-mediated hepatitis.

Immune-Mediated Endocrinopathies
- OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

*Histology-based chemotherapy; NSQ: pemetrexed + (carboplatin or cisplatin); SQ: paclitaxel + carboplatin.¹

PD-1=programmed death receptor-1.
SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-Mediated Nephritis with Renal Dysfunction
- OPDIVO and YERVOY can cause immune-mediated nephritis.

Immune-Mediated Dermatologic Adverse Reactions
- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information)

Other Immune-Mediated Adverse Reactions
- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: cardiac/vascular: myocarditis, pericarditis, vasculitis; nervous system: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation). Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; ocular: uveitis, iritis, and other ocular inflammatory reactions can occur; gastrointestinal: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; musculoskeletal and connective tissue: myositis/ polymyositis, rhabdomyolysis, and associated sequelae including renal failure; arthritis, polymyalgia rheumatica; endocrine: hypophysitis; other (hematologic/immune): hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: nervous system: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; cardiovascular: angorhythmia, temporal arteritis; ocular: blepharitis, episcleritis, orbital myositis, scintis; gastrointestinal: pancreatitis (1.3%); other (hematologic/immune): conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoaesthesia, psoriasis.

- Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions
- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.

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

Embryo-Fetal Toxicity
- Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of OPDIVO and YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone
- In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Lactation
- There is no data on the presence of OPDIVO or YERVOY in human milk. The effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

Serious Adverse Reactions
- In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea, colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myelotoxicity, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Common Adverse Reactions
- In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (33%), musculoskeletal pain (27%), diarrhea and colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).

Please see additional Important Safety Information for OPDIVO and YERVOY throughout and accompanying brief summary of US Full Prescribing Information for OPDIVO and YERVOY on the following pages.
INDICATIONS AND USAGE
Please also see Brief Summary for YERVOY® (ipilimumab) following OPDIVO® (nivolumab).

Cardiac/Vascular:
- Cardiac mortality
- Increase in median age of occurrence
- Increase in mortality
- Increase in length of stay
- Increase in cost of treatment
- Increase in patient safety

Gastrointestinal:
- Nausea
- Vomiting
- Diarrhea
- Constipation

Endocrine:
- Hyperthyroidism
- Hypothyroidism
- Diabetes mellitus

Musculoskeletal and Connective Tissue:
- Arthritis
- Myalgia

Psychiatric:
- Depression
- Insomnia

Respiratory, Thoracic, and Mediastinal:
- Pneumonitis
- Pleural effusion

Skin and Subcutaneous Tissue:
- Rashes
- Pruritus

Infections and Infestations:
- Infections and infestations

Nervous System:
- Headaches

Other
- Hypothyroidism

OPDIVO can cause immune-mediated hepatitis, which is defined as requiring use of steroids and no clear alternate etiology. The incidence of hepatitis is higher in patients who have received prior thoracic radiation.

In NSCLC, immune-mediated hepatitis occurred in 3% (88/3294) of patients treated with OPDIVO as a single agent in Phase II and III clinical trials. Of these patients, 96 (86.5%) of 109 were reported with elevated liver enzymes, and 13 (12.9%) were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.

In patients with advanced melanoma, immune-mediated hepatitis occurred in 1% (2/159) of patients treated with OPDIVO as a single agent in Phase I and II clinical trials. Of these patients, 1/2 were reported with elevated liver enzymes, and 1/2 were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.

In patients with advanced melanoma, immune-mediated hepatitis occurred in 3% (19/611) of patients treated with OPDIVO as a single agent in Phase III clinical trials. Of these patients, 12/19 were reported with elevated liver enzymes, and 7/19 were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.

In patients with melanoma, immune-mediated hepatitis occurred in 2% (2/111) of patients treated with OPDIVO as a single agent in Phase II clinical trials. Of these patients, 1/2 were reported with elevated liver enzymes, and 1/2 were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.

In patients with advanced melanoma, immune-mediated hepatitis occurred in 2% (2/111) of patients treated with OPDIVO as a single agent in Phase II clinical trials. Of these patients, 1/2 were reported with elevated liver enzymes, and 1/2 were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.

In patients with advanced melanoma, immune-mediated hepatitis occurred in 3% (36/1111) of patients treated with OPDIVO as a single agent in Phase III clinical trials. Of these patients, 28/36 were reported with elevated liver enzymes, and 8/36 were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.

In patients with advanced melanoma, immune-mediated hepatitis occurred in 2% (2/111) of patients treated with OPDIVO as a single agent in Phase II clinical trials. Of these patients, 1/2 were reported with elevated liver enzymes, and 1/2 were reported with jaundice. There was no apparent correlation between increased liver enzymes and the administration of OPDIVO.
Table 2: Laboratory Values Worsening from Baseline* Occurring in ≥20% of Patients on OPDIVO (nivolumab) and Ipilimumab - CHECKMATE-227

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Grades 1-4 (%)</th>
<th>Baseline Grades 3-4 (%)</th>
<th>Follow-up Grades 1-4 (%)</th>
<th>Follow-up Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>46</td>
<td>5</td>
<td>76</td>
<td>14</td>
</tr>
<tr>
<td>ALT</td>
<td>61</td>
<td>5</td>
<td>60</td>
<td>15</td>
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<tr>
<td>Total Bilirubin</td>
<td>70</td>
<td>9</td>
<td>74</td>
<td>16</td>
</tr>
<tr>
<td>Creatinine</td>
<td>48</td>
<td>6</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>40</td>
<td>15</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>36</td>
<td>10</td>
<td>40</td>
<td>9</td>
</tr>
</tbody>
</table>

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (OPDIVO and Ipilimumab group range: 494 to 566 patients) and chemistries group range: 469 to 542 patients.

Table 3: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doubllet Chemotherapy - CHECKMATE-9LA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>General Musculoskeletal Pain</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>General Nausea</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>General Diarrhea</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>General Constipation</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>General Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Abdominal pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Skin and Subcutaneous Tissue</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Rash, morbilliform rash</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Rash, papular rash</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Rash, pruritic rash</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Skin exfoliation</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Skin reaction</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Skin toxicity</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Stevens-Johnson syndrome</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Urticaria</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Nasal congestion</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Headache</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Diarrhea</td>
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<td>1</td>
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<tr>
<td>General Constipation</td>
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<td>1</td>
</tr>
<tr>
<td>General Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Abdominal pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Rash, morbilliform rash</td>
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<td>1</td>
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</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>General Urticaria</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4: Laboratory Values Worsening from Baseline* Occurring in ≥20% of Patients on OPDIVO (nivolumab) and Ipilimumab and Platinum-Doubllet Chemotherapy - CHECKMATE-9LA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Grades 1-4 (%)</th>
<th>Baseline Grades 3-4 (%)</th>
<th>Follow-up Grades 1-4 (%)</th>
<th>Follow-up Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Urea Nitrogen</td>
<td>40</td>
<td>15</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>Blood Creatinine</td>
<td>36</td>
<td>10</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Serum Calcium</td>
<td>48</td>
<td>6</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>Serum Magnesium</td>
<td>36</td>
<td>10</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Serum Phosphorus</td>
<td>36</td>
<td>10</td>
<td>40</td>
<td>9</td>
</tr>
</tbody>
</table>

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (OPDIVO and Ipilimumab group range: 494 to 566 patients) and chemistries group range: 469 to 542 patients.

Table 5: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doubllet Chemotherapy - CHECKMATE-9LA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
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</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>General Constipation</td>
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<td>2</td>
</tr>
<tr>
<td>General Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General Abdominal pain</td>
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<tr>
<td>General Rash, pruritic rash</td>
<td>12</td>
<td>1</td>
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<tr>
<td>General Skin exfoliation</td>
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<tr>
<td>General Skin reaction</td>
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<td>1</td>
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<td>General Skin toxicity</td>
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<tr>
<td>General Stevens-Johnson syndrome</td>
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<tr>
<td>General Constipation</td>
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<tr>
<td>General Vomiting</td>
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<tr>
<td>General Abdominal pain</td>
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<tr>
<td>General Urticaria</td>
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</tbody>
</table>
YERVOY® (ipilimumab), for intravenous use

**INDICATIONS AND USAGE**

YERVOY® (ipilimumab), in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, [see Dosage and Administration], with no EFR or ALK genomic tumor aberrations.

- YERVOY in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EFR or ALK genomic tumor aberrations.

**DOSAGE AND ADMINISTRATION**

**Patient Selection**

Select patients with metastatic NSCLC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression [see Clinical Studies (14.3) and Use in Specific Populations (8)].

**Infectious Workup**

YERVOY is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be an exhaustive list of all potential adverse reactions that may occur in any given patient. Immune-mediated adverse reactions may vary in severity and time of onset. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude other etiologies.

**Immune-Mediated Colitis**

YERVOY can cause immune-mediated colitis, which may be fatal. Cytoexsudative (USM) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude other etiologies.

**Immune-Mediated Dermatologic Adverse Reactions**

Immune-mediated dermatologic adverse reactions can also manifest after discontinuation of YERVOY. Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be indicative of underlying dermatologic adverse reactions, as defined by the National Institute of Allergy and Infectious Diseases guidelines. Treat susceptible conditions (e.g., bullous pemphigoid and lupus vulgaris) with high-dose systemic corticosteroids. Systemic corticosteroids may be adequate to treat mild to moderate non-bullous/necrolytic rash. Withhold or permanently discontinue YERVOY depending on severity [see Dosage and Administration (2.3) in Full Prescribing Information].

**Immune-Mediated Endocrinopathies**

- **Hypothyroidism**
  - YERVOY can cause immune-mediated hypothyroidism. Hypothyroidism can present with acute symptoms associated with mass effect such as headache, visual symptoms, or eyelid swelling. Immune-mediated hypothyroidism can be defined within 30 days of initiating YERVOY.
  - YERVOY can cause immune-mediated hypothyroidism. Immune-mediated hypothyroidism can also occur after discontinuation of YERVOY, within 30 days of last treatment with YERVOY.

**Risks Associated When Administered in Combination with Nivolumab**

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**Immune-Mediated Dermatologic Adverse Reactions**

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Increased creatinine | 26 | 1.2 | 23 | 0.6 | Leukopenia | 36 | 10 | 40 | 9 

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>YERVOY and Nivolumab</th>
<th>Platinum-Doublen Chemotherapy</th>
<th>YERVOY and Nivolumab</th>
<th>Platinum-Doublen Chemotherapy</th>
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<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
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<tr>
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<tr>
<td>B Lymphocyte</td>
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<td>2</td>
<td>12</td>
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</tr>
<tr>
<td>Natural Killer Cell</td>
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<tr>
<td>Total Leukocytes</td>
<td>24</td>
<td>6</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>

Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of major urinary obstruction and subcutaneous scrotal edema. Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hypothyroidism, hyperthyroidism, diabetes mellitus, hyperglycemia, or hypoglycemia.

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.

In a combined study of early-fetal and postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis through the first trimester apart from treatment. No treatment-related adverse events on reproduction were detected during the first two trimesters of pregnancy. Starting in the third trimester, administration of ipilimumab at doses ranging from opiuines approximately 2.6 to 7.2 times the human-exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and increased incidences of infant mortality in a dose-related manner (see Data). The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human data is known to cross the placental barrier and ipilimumab is an IgG. Therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Bristol-Myers Squibb at 1-844-583-7869.

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**MUSC Investigators Aim to Improve Safety and Efficacy of CAR T-cell Therapies**

*contributed by MUSC HOLLINGS CANCER CENTER*

A NEW PROJECT LED by investigators at the Medical University of South Carolina (MUSC) Hollings Cancer Center in Charleston could significantly decrease the adverse effects associated with chimeric antigen receptor (CAR) T-cell therapy and make the treatment available to more patients who could benefit.

Led by hematologist and oncologist Brian T. Hess, MD, and coleader of Hollings Cancer Center’s Cancer Immunology Research Program Shikhar Mehrotra, PhD, the project’s objectives include manufacturing a purified version of the CAR T cells that are used to treat patients with certain types of lymphoma and leukemia. In turn, investigators hypothesize that this will reduce the adverse effects associated with treatment and potentially make the treatment more effective. The therapy will be given to patients as part of a clinical trial, including those with lymphoma or leukemia for whom FDA-approved CAR T-cell therapies are not available (TABLE 1-4).

The project is supported in part by a $50,000 grant from LOWVELO, Hollings’ annual community event to raise money for lifesaving cancer research. The CAR T-cell-focused program is one of the first programs to benefit from the fund.

“The grant we’ve received from LOWVELO is a really great start to help us to get this project off the ground and to help us to treat our first patient,” Hess said.

Engineering CAR T-cell therapy begins by collecting a patient’s T cells, genetically modifying the collected cells to identify specific targets (such as CD19) on cancer cells, and then infusing them back into patients to fight their disease.

The clinical trial at Hollings will be open to adult patients with B-cell acute lymphoblastic leukemia (B-ALL) and certain patients with CD19-expressing non-Hodgkin lymphoma regardless of eligibility to receive FDA-approved products such as brexucabtagene autoleucel (Tecartus) or tisagenlecleucel (Kymriah).

As part of this trial, the team at Hollings are collaborating with investigators from Loyola University in Chicago, Illinois, to build on their existing technology by utilizing a specific cytokine protein (IL-12) in the manufacturing process of CAR T-cell products. In September 2018, Loyola and Loyola Medicine received a $250,000 grant from the Leukemia Research Foundation to develop purer, less toxic CAR T cells for the treatment of patients with leukemia and lymphoma.

Mehrotra, who is also scientific director of the Foundation for the Accreditation of Cellular Therapy-accredited Clean Cell Therapy Unit at MUSC and an associate professor in the Department of Surgery, said the MUSC project for developing CD19-directed CAR T-cell therapies was initiated through a collaboration with Michael Nishimura, PhD, at Loyola, who worked with the investigators to generate CD19-directed CAR T cells at MUSC’s clean cell facility. Nishimura is a professor of surgery, associate director of cancer center translational research, and program director of immunologic therapeutics at Loyola University Chicago Health Sciences.

“Our clinical partnership with [Dr Hess] will not only help to treat patients, but we are excited to gain more understanding of the complex biology of patient responses as we track these adoptively transferred CAR-engineered T cells,” Mehrotra said. “This will be an important advance for Hollings, where we strive to bring cutting-edge treatment for cancer patients. As they say, ‘It takes a village.’ The different basic science and clinical expertise that we have developed over many years at Hollings are all coming together to implement new strategies for cancer care. It is a great testimony to a big team effort and institutional leadership and vision.”

Hess, who is also an assistant professor at MUSC, agreed, noting that the treatment will improve not only patients’ outcomes but also their quality of life during treatment. “This new approach will hopefully improve the toxicity profile related to CAR T-cell infusion as well as make the CAR T cells more effective in fighting the lymphoma or leukemia,” he said. “We also hope that this trial improves the availability of this dynamic therapy to patients throughout South Carolina.”
A SHOT AT A CURE

Patients often are referred for CAR T-cell therapy when they have experienced multiple relapses and have few or any standard therapy options left to them. Although it does carry associated risks, CAR T-cell therapy offers hope to these patients.

“CAR T-cell therapy has been able to provide durable remissions and hopefully a cure to patients who otherwise have an extremely poor prognosis,” Hess said. “FDA-approved CAR T-cell therapies, as well as [products evaluated in this] upcoming trial, help [instill the] hope of offering cures to patients who otherwise would have very poor outcomes.”

Hollings first introduced CAR T-cell therapy to South Carolina in 2019, and it is the only center in the state with both an adult and a pediatric CAR T-cell program. In 2020, the therapy was used to treat 14 patients. In 2021, Hollings’ physicians expect to have treated between 40 and 50 patients, with continued growth on the horizon, thanks to new approvals to use the therapy in additional cancer types.

Nationwide, investigators are evaluating CAR T-cell therapies as a possible treatment option for patients with hematologic, brain, breast, gastrointestinal, lung, ovarian, pancreatic, and skin cancers.

Hess said Hollings is fortunate to have access to a clean cell facility, which is necessary to manufacture these cells, and to have the benefit of a multidisciplinary team to oversee a program of this scope.

“A patient’s journey from evaluation for CAR T [eligibility] to infusion of cells to the post CAR T-cell therapy care requires multidisciplinary expertise throughout Hollings, including cellular therapy coordinators, apheresis/cryopreservation nurses, clinic nurses, nurse practitioners, pharmacists, quality coordinators, physicians, etc, all of whom specialize in cellular therapy,” Hess explained. “We also rely on the expertise of other departments outside of Hollings, such as a partnership with the emergency department and the medical intensive care unit, which help to manage adverse effects of CAR T-cell therapy.”

By initiating this project and leveraging the center’s multidisciplinary team of investigators, Hess says he wants to learn more about the science behind CAR T-cell therapy to determine how to make it safer. He also would like to make the therapy more effective and applicable to additional cancer types, including solid tumors.

“Just like we need physicians to see patients and administer CAR T-cell therapy, we need investigators to be able to manufacture the best possible CAR T-cell product,” Hess said. “They are a vital partner in making this clinical trial available to patients. [Investigators are] also the team with whom we will collaborate to perform the science related to this study to advance the field and inform future studies.”

Mehrotra said he sees this project as the beginning of an array of promising trials. Generally, most patients’ T cells are collected and sent off to commercial laboratories for genetic engineering. The inhouse approach involving the creation of purer CAR T cells could help patients to avoid serious adverse effects and lower the cost of treatment, making it available for more patients with cancer.

“These are exciting times for cellular therapies and engineering autologous T cells with CARs [as we] recognize tumor antigen puts us at the forefront of treating cancers,” Mehrotra said. “We are excited to partner with [Dr Hess] and to be able to treat patients in the next 6 to 8 months with the first inhouse-generated CAR T-cell therapy. I am sure that once we get off the ground, similar strategies can be used for targeting other cancers.”

REFERENCES
Enhanced Grasp of Oncogenic Drivers Leads to Expanded Treatment Options in NSCLC

by KYLE DOHERTY

AN INCREASED UNDERSTANDING OF the biology of non–small cell lung cancer (NSCLC) has led to a significant increase in therapeutic options for patients, according to Lyudmila A. Bazhenova, MD, a medical oncologist and professor of medicine at the Moores Cancer Center at UC San Diego Health in California.

“The number of [known] oncogenic drivers [is] increasing every year,” Bazhenova said in an interview with OncologyLive®. “It’s important not to [under use] genotype [assays]—or to skip genotyping altogether—because the medications have fairly significant efficacy and it’s important not to miss an opportunity to provide these treatments to patients.”

Bazhenova highlighted the active areas of investigation for patients with NSCLC where advances have resulted in several new targeted agents that may improve personalized medicine for these patients.

KRAS

KRAS mutations are observed in approximately 30% of patients with NSCLC, and KRAS G12C alterations are seen in 13% of patients with lung adenocarcinoma. Because of the high affinity of KRAS for guanine triphosphate, the discovery of targeted therapies has previously proved to be challenging.1 Investigators have demonstrated promise with 2 novel small-molecule inhibitors, both targeting KRAS G12C: sotorasib (Lumakras), which received accelerated approval from the FDA in May, and adagrasib, which received a breakthrough therapy designation from the FDA in June.2,3

Sotorasib, a KRAS G12C inhibitor, was evaluated in the phase 1/2 CodeBreaK 100 trial (NCT03600883).4 Investigators enrolled 126 patients with NSCLC harboring a KRAS G12C mutation to the single-arm trial, and patients received oral sotorasib 960 mg once daily until disease progression.4 As of the March 15, 2021, data cutoff, the objective response rate (ORR) was 37.1% (95% CI, 28.6%-46.2%) among the 124 efficacy-evaluable patients, including 4 complete responses (CRs). At a median follow-up of 15.3 months, the median duration of response (DOR) was 11 months (95% CI, 6.9-not estimable [NE]) and the median progression-free survival (PFS) was 6.8 months (95% CI, 5.1-8.2). The median overall survival (OS) was 12.5 months (95% CI, 10.0-NE).4

In terms of safety, no fatal treatment-related adverse events (TRAEs) occurred. The most common TRAEs of any grade included diarrhea (31.7%), nausea (19.0%), and increased alanine aminotransferase (15.1%). TRAEs leading to dose modifications occurred in 22.2% of patients, and TRAEs that led to treatment discontinuation occurred in 7.1% of patients.4

The confirmatory phase 3 CodeBreak 200 trial (NCT04303780) evaluating sotorasib vs docetaxel in patients with pretreated KRAS G12C-mutant NSCLC is ongoing.

Adagrasib (MRTX849), a potent, covalent inhibitor of KRAS G12C, demonstrated clinical activity for this patient population in results from the phase 1/2 KRYSTAL-1 trial (NCT03785249). A total of 79 patients with pretreated NSCLC harboring a KRAS G12C mutation received adagrasib 600 mg twice daily.

Among 51 efficacy-evaluable patients, the ORR was 45% as of the August 30, 2020, data cutoff. Stable disease was reported in 26 patients. The median duration of treatment was 8.2 months.5 TRAEs of any grade were reported in 85% of patients. The most commonly reported TRAEs of any grade were nausea (54%), diarrhea (51%), and vomiting (35%). Grade 3/4 TRAEs occurred in 30% of patients, and 2% of patients experienced a grade 5 TRAE.5
The phase 3 KRISTAL-12 trial (NCT04685135) will evaluate the efficacy of adagrasib 600 mg vs docetaxel in patients with advanced NSCLC harboring a KRAS G12C mutation who have progressed during or after treatment with a platinum-based regimen and an immune checkpoint inhibitor. The study will enroll approximately 450 patients and is currently enrolling in the United States, Europe, and Asia.4

“The efficacy for patients with KRAS-mutant NSCLC is not as good as the efficacy for other oncogenic drivers,” Bazhenova noted. “[However], we are very excited about [these agents] because they’re the first drugs that we can use for these patients. But, certainly, we need to work on increasing the response rate mostly by utilizing combination treatments.”

**BRAF**

BRAF is altered in 4.5% of patients with NSCLC, 96% of these alterations being mutations. The most common BRAF mutations include BRAF activating (38%), BRAF V600E (37%), and BRAF inactivating (18%). Rearrangements account for 4% of BRAF alterations. Several agents have demonstrated significant efficacy for those with BRAF V600E, which occur at a rate comparable to the frequency of ALK, ROSI, or RET.7

The antitumor activity and safety of dabrafenib (Tafinlar), a potent and selective inhibitor of BRAF kinase activity, plus trametinib (Mekinist) were examined in a phase 2 trial (NCT01336634) that enrolled 57 adult patients with metastatic BRAF V600E-mutant NSCLC. Patients received oral dabrafenib 150 mg twice daily plus oral trametinib 2 mg once daily. The median age of the study population was 64 years (range, 41-88) and most patients had previously undergone 1 prior systemic regimen for metastatic disease (67%).8

At a median follow-up of 11.6 months (interquartile range [IQR], 8.8-15.2), the ORR was 63.2% (95% CI, 49.3%-75.6%) and 3.5% of patients achieved a CR. The median PFS was 9.7 months (95% CI, 6.9-19.6) and the median DOR was 9.0 months (95% CI, 5.8-17.6). The disease control rate (DCR) was 78.9% (95% CI, 66.1%-88.6%) and the median duration of treatment for both dabrafenib and trametinib was 10.6 months (IQR, 4.2-12.2).8

In terms of safety, serious AEs were reported in 56% of patients. AEs leading to treatment discontinuation occurred in 12% of patients, and AEs leading to dose reduction were seen at a rate of 35%. Common AEs of any grade included pyrexia (46%), nausea (40%), and vomiting (35%).8

Investigators evaluated the efficacy of a vemurafenib (Zelboraf), a BRAF inhibitor, in patients with metastatic or unresectable locally advanced malignancies harboring BRAF genomic alterations in the phase 2 AcSé trial (NCT02304809). The study population included 118 patients in the NSCLC cohort; 101 of these patients presented with a BRAF V600E mutation. Vemurafenib was administered at 960 mg twice daily.

Most patients in both the BRAF V600E cohort and the BRAF cohort had previously received chemotherapy (79.3% vs 82.4%, respectively).9

After a median follow-up of 23.9 months (95% CI 19.8-25.0), among 100 efficacy-evaluable patients with BRAF V600E mutations, the ORR was 44.8%. The median DOR was 6.4 months (95% CI, 5.1-7.3), the median PFS was 5.2 months (95% CI, 3.8-6.8), and the median OS was 10 months (95% CI, 6.8-15.7).9

The median PFS in the in the efficacy-evaluable BRAF cohort (n = 15) was 1.8 months (95% CI, 1.4-2.1) and the median OS was 5.2 months (95% CI, 2.8-18.7). No objective response was observed in the cohort and enrollment was subsequently stopped.9

In the BRAF V600E cohort, the most common TRAEs of any grade were asthenia (56%), decreased appetite (46%), acneiform dermatitis (37%), and nausea and diarrhea (35% each). Treatment was discontinued because of toxicity for 24 patients in the BRAF V600E cohort and 3 patients in the BRAF cohort. Grade 5 toxicities were reported in 3 patients, due individually to dehydration, pneumonia, and neuropenic sepsis.9

**MET**

MET amplifications are reported in 3% to 7% of patients with NSCLC. Rare but actionable mutations within MET include MET exon 14 skipping mutations. which occur at a rate of approximately 3% in NSCLC. Two agents—capmatinib (Tabrecta) and tepotinib (Tepmetko)—have received accelerated FDA approval in the past 2 years.10,11

Capmatinib, a selective MET inhibitor, was evaluated in adult patients with EGFR wild-type, advanced NSCLC in the phase 2 Geometry Mono-1 study (NCT02414139). Patients received oral capmatinib 400 mg twice daily. The study included 97 patients with NSCLC with a MET exon 14 skipping mutation and 210 patients with NSCLC with a MET amplification.12

Previously treated patients with harboring a MET exon 14 skipping mutation (n = 69) had an ORR of 41% (95% CI, 29%-53%) and a median DOR of 9.7 months (95% CI, 5.6-13.0). Treatment-naïve patients with NSCLC harboring a MET exon 14 skipping mutation (n = 28) achieved an ORR of 68% (95% CI, 48%-84%) and a median DOR of 12.6 months (95% CI, 5.6-NE).12

### TABLE. Response Rates of Targeted Agents4,5,8-9,12-15,17

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<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotorasib</td>
<td>KRAS</td>
<td>37.1% (28.6%-46.2%)</td>
</tr>
<tr>
<td>Adagrasib</td>
<td>KRAS</td>
<td>45%</td>
</tr>
<tr>
<td>Dabrafenib plus trametinib</td>
<td>BRAF</td>
<td>63.2% (49.3%-75.6%)</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>44.8%*</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>MET</td>
<td>32% (21%-45%)</td>
</tr>
<tr>
<td>Capmatinib</td>
<td>MET</td>
<td>Pretreated: 4% (95% CI, 29%-53%)</td>
</tr>
<tr>
<td>Tepotinib</td>
<td>MET</td>
<td>Treatment-naïve: 68% (48%-84%)</td>
</tr>
<tr>
<td>Savolitinib</td>
<td>MET</td>
<td>46% (36%-57%)</td>
</tr>
<tr>
<td>Trastuzumab deruxtecan</td>
<td>HER2</td>
<td>55% (44%-65%)</td>
</tr>
</tbody>
</table>

ORR, objective response rate.

*CI not available.

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The phase 2 VISION trial (NCT02864992) evaluated the efficacy of the highly selective MET inhibitor tepotinib in adult patients with advanced NSCLC with MET exon 14 skipping alterations or MET amplification. Tepotinib was administered at a dose of 500 mg, twice daily. The median age of patients in the efficacy population (n = 99) was 74 (range, 41-94).13

The ORR in the efficacy population was 46% (95% CI, 36%-57%) and the median DOR was 11.1 months (95% CI, 7.2-NE). The median PFS was 8.5 months (95% CI, 6.7-11.0).13 In terms of safety, among the 152 patients in the safety population, 89% experienced an AE of any grade. The most common AEs of any grade were peripheral edema (63%), nausea (26%), and diarrhea (22%). Serious AEs related to tepotinib were reported in 15% of patients and led to permanent discontinuation of treatment in 11% of patients.13

The antitumor activity and safety of crizotinib (Xalkori), a multikinase inhibitor with potent activity against MET, was examined in a phase 1 PROFILE 1001 cohort of the phase 1 PROFILE 1001 study (NCT00585195). Crizotinib was administered orally at a dose of 250 mg twice daily (NCT00585195). Crizotinib was administered intravenously at a dose of 6.4 mg/kg.17

The ORR among the efficacy-evaluable patients (n = 65) was 32% (95% CI, 21%-45%); 5% achieved a CR. The median age of the study population was 72 (range, 34-91) and the median time to response was 7.6 weeks (range, 3.7-16.3).14 The most common TRAEs of any grade were edema (51%), vision disorder (45%), and nausea (41%). TRAEs associated with a dose reduction or permanent treatment discontinuation occurred in 38% and 7% of patients, respectively.14

Savolitinib, a highly selective MET tyrosine kinase inhibitor, was examined in patients with pulmonary sarcomatoid carcinoma and other types of NSCLC harboring MET exon 14 skipping mutations in a phase 2 study (NCT02897479). Oral savolitinib 600 mg for patients weighing at least 50 kg or 400 mg for patients weighing less than 50 kg was given once daily until disease progression or intolerable toxicity. The median age of treated patients (N = 70) was 68.7 years (range, 51.7-85.0).15 Among 61 efficacy-evaluable patients, the ORR was 49.2% (95% CI, 36.1%-62.3%) and the DCR was 93.4% (95% CI, 84.1%-98.2%). The median DOR was 9.6 months (95% CI, 5.5-not reached). The median treatment duration was 6.8 months (range, 0.2-37.3).15

Most patients experienced an AE of any grade (98.6%) and 41.4% experienced an AE of grade 3 or higher. TRAEs that led to dose discontinuation were reported in 14.3% of patients.15

**TABLE.** Response Rates of Targeted Agents4,5,8,9,12-15,17

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>~25%</td>
</tr>
<tr>
<td>EGFR</td>
<td>~17%</td>
</tr>
<tr>
<td>ALK</td>
<td>~5%-7%</td>
</tr>
<tr>
<td>METx14</td>
<td>~3%-4%</td>
</tr>
<tr>
<td>HER2</td>
<td>~2%-3%</td>
</tr>
<tr>
<td>ROS1</td>
<td>~1%-2%</td>
</tr>
<tr>
<td>RET</td>
<td>~1%-2%</td>
</tr>
<tr>
<td>BRAF</td>
<td>~1%-2%</td>
</tr>
<tr>
<td>MEK</td>
<td>1%</td>
</tr>
<tr>
<td>NRAS</td>
<td>~1%</td>
</tr>
<tr>
<td>NTRK1/2/3</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

**Other/unknown | ~31%**

METx14, MET exon 14 skipping mutation; NSCLC, non–small cell lung cancer.

**HER2**

Investigators are also actively evaluating the role of targeting HER2 aberrations in patients with NSCLC. HER2 overexpression occurs in approximately 5% of patients with NSCLC. HER2 mutations are seen in 1% to 5% of patients with NSCLC, and the most common mutations occur in exon 20 (80%-90% of all HER2 mutations).14

Fam-trastuzumab deruxtecan-nxki (Enhertu), a HER2-directed antibody-drug conjugate (ADC) that has demonstrated efficacy in breast and gastric cancers, was evaluated in patients with HER2-mutant NSCLC in the phase 2 DESTINY-Lung01 trial (NCT03505710). The trial enrolled a total of 91 patients and the median age was 60 (range, 29-88). Trastuzumab deruxtecan was administered intravenously at a dose of 6.4 mg/kg.17

The ORR was 55% (95% CI, 44%-65%) and 1 patient achieved a CR. The median DOR was 9.3 months (95% CI, 5.7-14.7) and the median time to response was 1.5 months (range, 1.2-9.3). The median PFS was 8.2 months (95% CI, 6.0-11.9) and the median OS (95% CI, 13.8-22.1).17

In terms of safety, 97% of patients experienced an AE; the most common AEs of any grade were nausea (73%), fatigue (53%), and alopecia (46%). AEs leading to dose reduction occurred in 34% of patients and dose interruption occurred in 32% of patients. Adjudicated drug-related interstitial lung disease of any grade was reported in 26% of patients.17

“We still do not know a lot about resistance to ADCs,” Bazhenova said. “These are new medications for us in the thoracic oncology space. For HER2 exon 20 insertions, hopefully an ADC is approved at some point. The unmet need here is to understand what type of resistance patients develop, and to get a better understanding of how to prognosticate patients for interstitial lung disease.”

Bazhenova noted that understanding mechanisms of resistance extends beyond ADCs. “At this point, we don’t yet know what to do [in terms of] resistance to medications,” she said, adding that investigative efforts are under way to optimize sequencing and combination strategies.
Nectin-4 Emerges as a Therapeutic Target in Urothelial Carcinoma and Beyond

by JANE DE LARTIGUE, PhD

IN JULY 2021, the FDA granted full regulatory approval to enfortumab vedotin-ejfv (Padcev) for the treatment of patients with relapsed or refractory advanced/metastatic urothelial carcinoma.1 Previously awarded accelerated approval for this indication in 2019, enfortumab vedotin is the first drug to target the nectin-4 protein, a key regulator of cell adhesion.3,4

An antibody-drug conjugate (ADC), enfortumab vedotin exploits the high levels of nectin-4 expression in urothelial carcinoma to enable targeted deployment of a cytotoxic warhead in tumor cells.5 Specifically, enfortumab vedotin is approved for patients with locally advanced/metastatic urothelial carcinoma who have been previously treated with a PD-1/PD-L1 immune checkpoint inhibitor (ICI) and platinum-containing chemotherapy or are ineligible for cisplatin-containing chemotherapy after receiving 1 or more prior lines of therapy.1

Beyond enfortumab vedotin, the development of nectin-4–targeted drugs is in its infancy; other agents are in the preclinical or very early clinical stages of development. However, burgeoning interest in this target reflects the potential oncogenic role of nectin-4 across a broad range of malignancies.3,6

Furthermore, there is growing appreciation of the role of nectins in the antitumor immune response through their interaction with immune checkpoint receptors, including TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains).5,7

Most ongoing clinical trials exploring nectin-4 as a target involve studies of enfortumab vedotin and its potential synergy with ICIs in bladder cancer, while several other early-phase studies are testing novel agents in solid tumors (TABLE). Meanwhile, agonistic nectin-4–specific monoclonal antibodies could have ICI functionality in their own right.8

AN IDEAL TARGET

The nectin family of proteins, whose name derives from the Latin necto, meaning “to connect,” are cell adhesion molecules that are essential to forming physical connections between neighboring cells to enable intercellular communication, migration, and other vital cellular processes.3,5

Among the 4 human nectin proteins, nectin-4 is unique in that its expression is largely restricted to placental and embryonic tissues. Importantly, however, in contrast to healthy adult tissue, many types of cancer have high nectin-4 expression.3,5

In urothelial carcinoma, moderate to high levels of nectin-4 were observed in 60% of bladder cancer samples in 1 study9 and in 34% of upper tract urothelial carcinoma samples in another.10 In upper tract urothelial carcinoma, high levels of nectin-4 were associated with a significantly higher risk of progression (P = .03) and cancer-specific mortality (P = .04) and were an independent

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TABLE. Ongoing Clinical Development of Drugs Targeting Nectin-4

| Indication (trial name; Clinicaltrials.gov identifier) | [Note: For complete details on all ongoing clinical trials, please visit Clinicaltrials.gov.]
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfortumab vedotin-ejfv (Padcev)</td>
</tr>
<tr>
<td>Phase 3</td>
</tr>
<tr>
<td>+ durvalumab +/- tremelimumab for perioperative treatment of MIBC in cisplatin-ineligible patients undergoing radical cystectomy (VOLGA; NCT04960709)</td>
</tr>
<tr>
<td>+ pembrolizumab vs chemotherapy alone in treatment-naive, locally advanced/metastatic urothelial carcinoma (EV-302; NCT04223856)*</td>
</tr>
<tr>
<td>+ pembrolizumab and surgery vs surgery alone or with pembrolizumab for perioperative treatment of MIBC in cisplatin-ineligible patients (KEYNOTE-905/ EV-303; NCT03924895)*</td>
</tr>
<tr>
<td>+ pembrolizumab for perioperative treatment vs neoadjuvant chemotherapy in MIBC (EV-304; NCT04700124)</td>
</tr>
<tr>
<td>+ sitravatinib in advanced/metastatic solid tumors (NCT04887870)</td>
</tr>
<tr>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Monotherapy for previously treated advanced/metastatic solid tumors (EV-202; NCT04225117)</td>
</tr>
<tr>
<td>Phases 1 and 1/2</td>
</tr>
<tr>
<td>Monotherapy for previously treated metastatic CRPC (ENCORE; NCT04754191)*</td>
</tr>
<tr>
<td>+ pembrolizumab +/- chemotherapy as first- and/or second-line treatment for advanced/metastatic urothelial carcinoma or in the neoadjuvant or perioperative setting for MIBC (EV-103; NCT03288545)</td>
</tr>
<tr>
<td>+ avelumab in advanced/metastatic urothelial carcinoma that progressed during or following platinum-based chemotherapy (MORPHEUS-US; NCT03869190)</td>
</tr>
<tr>
<td>+ erdafitinib (FGFR inhibitor) in previously treated advanced/metastatic FGFR2/3-mutant urothelial carcinoma (NCT04963153)*</td>
</tr>
<tr>
<td>Monotherapy via intravesical administration in NMIBC (EV-104; NCT05014139)*</td>
</tr>
<tr>
<td>+ sacituzumab govitecan-hzi in previously treated metastatic urothelial carcinoma (DAD; NCT04724018)</td>
</tr>
<tr>
<td>+ cabilizumab in advanced/metastatic urothelial carcinoma (NCT04878029)</td>
</tr>
<tr>
<td>BT8009—phase 1/2</td>
</tr>
<tr>
<td>+/- nivolumab in previously treated, nectin-4—expressing, advanced solid tumors (BT8009-100; NCT04561362)</td>
</tr>
<tr>
<td>Nectin-4/FAP—targeted CAR T cells—phase 1</td>
</tr>
<tr>
<td>Monotherapy in nectin-4—expressing advanced solid tumors (NCT03932565)</td>
</tr>
</tbody>
</table>

CAR, chimeric antigen receptor; CRPC, castration-resistant prostate cancer; FAP, fibroblast activation protein; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

*A third arm of the trial testing enfortumab vedotin plus pembrolizumab and cisplatin or carboplatin is not recruiting patients.

*Survey is defined as radical cystectomy plus pelvic lymph node dissection.

*Trial is not yet recruiting participants.
predictor of disease progression in high-risk disease (HR, 3.32; 95% CI, 1.20-7.98; \( P = .03 \)).

Other cancer types in which nectin-4 overexpression has been found in a significant portion of samples include breast, ovarian, cervical, colorectal, esophageal, gastric, lung, liver, and thyroid cancer. Studies have suggested that nectin-4 expression may predict poor prognosis in several types of cancer; however, its analytical and clinical validity have not been fully established and its clinical utility as a prognostic marker remains to be confirmed.\(^5,6\)

High nectin-4 expression is associated with increased tumor size, grade, and invasiveness, as well as reduced patient survival, in some cancer types. In addition, nectin-4 overexpression may be linked to chemotheraphy resistance.\(^5,6,10\) A recent study also demonstrated that nectin-4 expression was upregulated in BRAF inhibitor-resistant melanoma cells.\(^90\)

As a result of its cancer-specific expression, nectin-4 has emerged as a highly promising therapeutic target. The main focus of drug development has been in advanced/metastatic urothelial carcinoma, in which 5-year survival rates are abysmally low despite the availability of novel immunotherapeutic options.\(^2,21\)

The standard of care for patients with advanced/metastatic urothelial carcinoma is platinum-based chemotherapy; however, a substantial number of patients are ineligible for chemotherapy. Patients with recurrent disease or whose tumors express PD-L1 may be treated with ICIs, but only a minority of patients experience durable responses; response rates are particularly low among patients with visceral metastases.\(^2,21\)

**FILLING A NICHE IN BLADDER CANCER**

Enfortumab vedotin, formerly ASG-22CE, is an ADC composed of a nectin-4-targeted monoclonal antibody conjugated via a cleavable linker to a microtubule-disrupting cytotoxic drug, monomethyl auristatin E (MMAE). It exploits nectin-4 expression in urothelial carcinoma to target the delivery of MMAE to tumor cells (FIGURE\(^21\)). Once the nectin-4 antibody component of the drug binds to nectin-4 on the membrane, the ADC is taken up into the cell, and the linker is cleaved within the lysosome, releasing MMAE, which binds to tubulin, disrupting microtubule assembly and driving cell cycle arrest and apoptosis.\(^5,6,21\)

Accelerated approval of enfortumab vedotin for the treatment of locally advanced/metastatic urothelial carcinoma in 2019\(^9\) was based largely on the results of 2 clinical trials, EV-101 and EV-201.\(^21\) EV-101 (NCT02091999) was a phase 1 dose-escalation and dose-expansion study of enfortumab vedotin in patients with previously treated advanced/metastatic solid tumors.\(^22\)

Initially, trial eligibility requirements included positive tumor nectin-4 expression per immunohistochemistry (IHC) analysis; however, the protocol was amended to remove this criterion after nectin-4 expression was identified in almost all samples (median IHC H-score, 290; range, 0-300). In cohort A, patients were treated with enfortumab vedotin monotherapy at escalating doses up to 1.25 mg/kg on days 1, 8, and 15 of 28-day cycles. In cohort B, dose expansion was performed in 3 patient populations: those with urothelial carcinoma, non-small cell lung cancer, or ovarian cancer. Cohort C involved dose expansion in patients with metastatic urothelial carcinoma that had progressed following ICI therapy.\(^22\)

Among the 112 patients with metastatic urothelial carcinoma who were treated with enfortumab vedotin at 1.25 mg/kg, the overall response rate (ORR) was 43% (95% CI, 33.6%-52.6%), with a median duration of response (DOR) of 7.4 months (95% CI, 5.6-9.6) and median overall survival (OS) of 12.3 months (95% CI, 9.3-15.3). Similar response rates were observed across all patient subgroups, including patients aged 75 years or older, those with liver metastases, and those with upper tract disease. The most common treatment-related adverse events (TRAEs) were rash, peripheral neuropathy, fatigue, alopecia, and nausea, predominantly grade 1 or 2 in severity.\(^22\)

EV-201 (NCT03219333) was a phase 2 single-arm trial in which enfortumab vedotin was tested in patients with metastatic urothelial carcinoma who had been previously treated with both platinum-based chemotherapy and ICIs (cohort 1) or with an ICI only (cohort 2). Patients were treated with a dose of 1.25 mg/kg on days 1, 8, and 15 of 28-day cycles. Although nectin-4 positivity was not a requirement for enrollment, nectin-4 expression (median IHC H score, 290; range, 14-300) was identified in 100% of the 120 patient samples that were collected.\(^23\)

In cohort 1 (n = 125), the ORR was 44% (95% CI, 35.1%-53.2%), including complete responses (CRs) in 12% of patients, with a median DOR of 7.6 months (95% CI, 4.93-7.46). Similar ORRs were observed across prespecified patient subgroups, including patients with liver metastases. The most common TRAEs were fatigue, alopecia, decreased...
NECTIN-4 is a cell adhesion molecule (CAM) that regulates the formation of physical connections between cells, facilitating a variety of important cellular processes and assisting in the development and maintenance of tissues and organs.¹⁻³

There are 4 nectins (nectin-1 through -4) in mammalian cells. The NECTIN1-4 genes that encode them were originally called poliovirus receptor-like 1-4 (PVRL1-4); this reflects the history of these proteins, which were originally discovered as receptors exploited by viruses to gain entry into cells.¹⁻³

Along with 5 nectin-like molecules (Necl-1 through -5), the nectins make up the immunoglobulin (Ig) superfamily of CAMs (FIGURE). These transmembrane proteins share a characteristic extracellular region composed of 3 Ig-like domains.¹⁻³

Through these domains, these proteins dimerize on the surface of the same cell (cis-dimerization) and subsequently form trans-dimers with nectins and Necls on opposing cells to bring about cell-cell contact. The dimers can be either homophilic (between 2 proteins of the same type, eg, 2 nectin-4 molecules) or heterophilic (between 2 different proteins, eg, nectin-4 and nectin-1).¹⁻³

Studies suggest that heterophilic trans-interactions are stronger than homophilic ones. Furthermore, whereas homophilic interactions are thought to function predominantly in cell-cell adhesion, heterophilic interactions may be involved in a range of other cell functions. Indeed, in addition to partnering up with nectin family members, nectins and Necls can interact with members of other protein families, perhaps most notably immunomodulatory proteins.²⁻⁴

Through their cytoplasmic tail, each of the nectins binds to an intracellular adaptor protein called afadin, which is an F-actin–binding protein. The resulting nectin-afadin complex then associates with the filamentous actin bundles that form the central structural component of the cell cytoskeleton, helping to stabilize and strengthen the adhesion site. The cytoplasmic tails of the Necls lack this afadin-binding motif.¹⁻³

In cell adhesion, nectins can function either independently or in concert with members of a second family of CAMs, the cadherins. There are several key differences between these 2 protein families. Cadherins act in a calcium-dependent fashion, but nectin dimerization is calcium independent. Additionally, cadherins function only in the adhesion of cells of the same type, whereas nectins can also function in heterotypic cell adhesion.¹⁻³

Nectin-4 differs from other members of the nectin family in that it is predominantly expressed during development, although it is weakly or moderately expressed in some tissue types in adults, including bladder, skin, and breast. Importantly, however, nectin-4 is highly expressed in numerous types of cancer.¹⁻⁵ Immunohistochemical analysis of more than 2000 patient samples across 7 cancer types (bladder, breast, lung, pancreatic, head and neck, and esophageal cancers) identified nectin-4 expression in over two-thirds of cases, with more pronounced staining in bladder and breast tumor specimens.⁵

In particular, more than 60% of cases of urothelial carcinoma, the most common type of bladder cancer, were shown to express moderate to high levels of nectin-4.⁶ In this and many other types of cancer, nectin-4 expression has also been linked to patient prognosis.¹⁻⁷ Thus, nectin-4 has emerged as a promising therapeutic target in cancer.

Development of nectin-4–targeted antibodies that guide the cancer-specific delivery of cytotoxic payloads in the form of antibody-drug conjugates led to the FDA approval of enfortumab vedotin-ejfv (Padcev). The agent, which received full approval in July 2021, is indicated for patients with locally advanced or metastatic urothelial carcinoma who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy or are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more prior lines of therapy.⁸⁻⁹

For a full list of references, see the article at OncLive.com.
ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.¹⁻¹⁰

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.—¹¹

INDICATION

RYBREVANT® (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions

RYBREVANT® can cause rash (including dermatitis aciform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

References:


¹¹. Based on Kaplan-Meier estimates. Based on Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).
In a multicenter, open-label, multicohort study, results of tough-to-treat disease

Results for tough-to-treat disease

- 3.7% of patients achieved a CR
- 36% of patients achieved a PR

Efficacy was evaluated by ORR and DOR

MEDIAN DOR WAS 11.1 MONTHS

(95% CI: 6.9, NE)

The safety of RYBREVT\textsuperscript{\textregistered} was evaluated in the CHRYSLIS* study (n=129):• The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and increased sodium (4%).

Please see Brief Summary of full Prescribing Information for RYBREVT\textsuperscript{\textregistered} on subsequent pages.


CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non–small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVT\textsuperscript{\textregistered} based on severity.

Ocular Toxicity

RYBREVT\textsuperscript{\textregistered} can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVT\textsuperscript{\textregistered}. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVT\textsuperscript{\textregistered} based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVT\textsuperscript{\textregistered} can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVT\textsuperscript{\textregistered}.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and increased sodium (4%).

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RYBREVANThcp.com

CR: complete response; DOR: duration of response; EGFR: epidermal growth factor receptor; IRR: infusion-related reaction; mNSCLC: metastatic non–small cell lung cancer; NE: not estimable; ORR: overall response rate; PR: partial response.
**Adverse Reactions**

The following adverse reactions are discussed elsewhere in the labeling:

- **Infusion-Related Reactions** [see Warnings and Precautions]
- **Interstitial Lung Disease/Pneumonitis** [see Warnings and Precautions]
- **Dermatologic Adverse Reactions** [see Warnings and Precautions]
- **Ocular Toxicity** [see Warnings and Precautions]

**Clinical Trials Experience**

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

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSLIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 800 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥2% of patients included rash and paronychia.

The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

**Interpretation of Laboratory Data**

Based on the safety population [see Adverse Reactions], abnormalities (≥2%) were decreased lymphocytes, decreased albumin, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.
**Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSLIS**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVANT+ (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33</td>
</tr>
<tr>
<td>Edema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;1&lt;/sup&gt;</td>
<td>37</td>
</tr>
<tr>
<td>Cough&lt;sup&gt;1&lt;/sup&gt;</td>
<td>25</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Stomatitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Headache&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Rash: acne, dermatitis, dermatitis acniform, eczema, eczema asthmatoid, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis
<sup>b</sup> Fatigue: asthenia, fatigue
<sup>c</sup> Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
<sup>d</sup> Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
<sup>e</sup> Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
<sup>1</sup> Dyspnea: dyspnea, dyspnea exertional
<sup>2</sup> Cough: cough, productive cough, upper airway cough syndrome
<sup>3</sup> Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
<sup>4</sup> Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
<sup>5</sup> Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
<sup>6</sup> Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
<sup>7</sup> Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

**Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSLIS**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYBREVANT+ (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>79</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

**Immunogenicity**

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

In CHRYSLIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

**Animal Data**

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in...
multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

**Lactation**
**Risk Summary**
There are no data on the presence of amivantamab-vmjw in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

**Females and Males of Reproductive Potential**
RYBREVANT can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

**Pregnancy Testing**
Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

**Contraception**
**Females**
Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

**Pediatric Use**
The safety and efficacy of RYBREVANT have not been established in pediatric patients.

**Geriatric Use**
Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 8% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

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

**Infusion-Related Reactions**
Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions [see Warnings and Precautions].

**Interstitial Lung Disease/Pneumonitis**
Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [see Warnings and Precautions].

**Dermatologic Adverse Reactions**
Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT [see Warnings and Precautions]. Advise patients to apply alcohol free emollient cream to dry skin.

**Ocular Toxicity**
Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated [see Warnings and Precautions].

**Paronychia**
Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia [see Adverse Reactions].

**Embryo-Fetal Toxicity**
Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. [see Warnings and Precautions, Use in Specific Populations].

**Lactation**
Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose [see Use in Specific Populations].

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appetite, dysgeusia, and peripheral neuropathy. Results from cohort 2 (n = 89) were also recently published; at a median follow-up of 13.4 months, the ORR was 52% (95% CI, 41%-62%), with CRs in 20% of patients.

FULL APPROVAL SECURED

Continued approval of enfortumab vedotin was premised on the demonstration of confirmed efficacy in randomized phase 3 trials. In the phase 3 EV-301 trial (NCT03474107), enfortumab vedotin was compared with standard chemotherapy in patients (n = 608) with locally advanced or metastatic urothelial carcinoma previously treated with platinum-based chemotherapy and an ICI. Patients were randomized 1:1 to enfortumab vedotin at a dose of 1.25 mg/kg on days 1, 8, and 15 of 28-day cycles or investigator’s choice of chemotherapy (docetaxel; n = 117, paclitaxel; n = 112, or vinflunine [where approved for use]; n = 78) administered on day 1 of 21-day cycles.

At a median follow-up of 11.1 months, enfortumab vedotin was found to significantly improve OS and progression-free survival (PFS) compared with chemotherapy in this patient population, reducing the risk of death by 30% and the risk of progression or death by 38%. Median OS was 12.88 months (95% CI, 10.58-15.21) in the enfortumab vedotin arm compared with 8.97 months (95% CI, 8.05-10.74) in the chemotherapy arm (HR, 0.70; 95% CI, 0.56-0.89; P < .001), and median PFS was 5.55 months (95% CI, 3.52-3.94) vs 3.71 months (95% CI, 3.52-3.94), which translated into an HR of 0.62 (95% CI, 0.51-0.75; P < .001). Patients treated with enfortumab vedotin also had a significantly higher ORR (40.6% vs 17.9%; P < .001) and a numerically higher CR rate (4.9% vs 2.7%).

The incidence of TRAEs of any grade (93.9% vs 91.8%) or of grade 3 and higher (51.4% vs 49.8%), as well as the rates of dose reduction, interruption, and discontinuation resulting from TRAEs, were similar in the 2 study arms. The most common grade 3 and higher TRAEs experienced by patients treated with enfortumab vedotin were maculopapular rash, fatigue, decreased neutrophil count, and neutropenia.

In an update presented at the European Society for Medical Oncology Congress 2021, findings showed that the survival benefit associated with enfortumab vedotin treatment was maintained across hard-to-treat patient subgroups, including patients aged 65 years and older and those with liver metastases, upper tract disease, and lack of response to prior ICI therapy.

In numerous ongoing clinical trials, investigators are evaluating the potential of enfortumab vedotin in the frontline setting for patients with advanced/metastatic urothelial carcinoma (EV-302; NCT04223856), as well as earlier in the course of disease in the perioperative setting (VOLGA; NCT04960709 and EV-304; NCT04700124).

Results from a cohort of patients enrolled in the ongoing EV-103 trial (NCT03288545) were recently published. EV-103 is a phase 1/2 trial evaluating enfortumab vedotin as monotherapy or in combination with other cancer drugs as first- and second-line treatment for patients with advanced/metastatic disease. After more than 2 years of follow-up, 45 cisplatin-ineligible patients who were treated with the combination of enfortumab vedotin and the PD-1 ICI pembrolizumab (Keytruda), in the frontline setting had an ORR of 73.3% (95% CI, 58.1%-85.4%), including CRs in 17.8% of patients, with a median DOR of 25.6 months (95% CI, 8.3-not reached) and median PFS of 12.3 months (95% CI, 8.0-not reached). Among patients with liver metastases, the ORR was 57.1%. The most common TRAEs were peripheral neuropathy, fatigue, and alopecia.

On the basis of these results, this combination was granted a breakthrough therapy designation by the FDA for the frontline treatment of patients with cisplatin-ineligible metastatic urothelial carcinoma.

AN IMMUNOMODULATORY ROLE

An increasingly recognized aspect of nectin family members is their role in immune modulation. Several nectins and nectin-like (Necl) molecules act as ligands for costimulatory and coinhibitory immune checkpoint receptors, and in recent years, the nectin family banner has been widened to encompass these receptors, most notably TIGIT.

TIGIT, a coinhibitory immune checkpoint receptor expressed on the surface of multiple immune cell types, exerts an immunosuppressive function. Alongside the costimulatory receptor CD226, TIGIT forms an immune checkpoint pathway that is analogous to the prototypical CD28/CTLA-4 checkpoint pathway. The ligands for TIGIT include CD112 (also known as nectin-2) and CD155 (Necl-5).

TIGIT has emerged as a promising target for the next generation of ICIs. Several TIGIT-targeted drugs are in clinical development, including Roche’s tiragolumab (MTIG719A) and Merck’s vistobolimab (MK-7684). A recent study identified nectin-4 as a novel ligand for TIGIT. Unlike other TIGIT ligands, which bind to additional receptors, nectin-4 appears to exclusively bind to TIGIT; this interaction was shown to inhibit the activity of natural killer cells.

Thus, in addition to providing specificity in tumor targeting, nectin-4-targeted therapies could also prove to have immunotherapeutic properties. The vast majority of ongoing clinical trials of enfortumab vedotin and development of novel nectin-4-targeted therapies are focusing on combining these drugs with ICIs in the hopes of eliciting synergistic activity.

Agents in development include Bicycle Therapeutics’ BT8009, whose design is similar to an ADC. The agent is conjugated to an MMAE but uses the company’s proprietary bicyclic peptides instead of an antibody to target nectin-4. Investigators hypothesize that the more rapid plasma clearance achieved by the small bicyclic peptide will reduce BT8009’s systemic toxicity compared with bulkier antibody-based agents.

Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.

For a full list of references, see the article at OncLive.com.
Novel Agents Shake Up Myelodysplastic Syndrome Treatment Landscape

by CHRISTINA T. LOGUIDICE

**MYELODYSPLASTIC SYNDROME (MDS)** refers to a heterogeneous group of closely related clonal disorders of hematopoietic stem cells that lead to dysplasia and ineffective hematopoiesis in the bone marrow, with older patients (> 65 years) most frequently affected. The disease course is variable and not all patients may require treatment initially, particularly if they are asymptomatic. In 2017, the World Health Organization published a revised classification of myeloid neoplasms to incorporate genetic information, which resulted in broadening the subset of cases classified as MDS with ring sideroblasts, and to improve patient risk stratification to enable better overall treatment. More recently, several agents for specific patient subgroups have been approved by the FDA, including for patients with very low-risk to high-risk MDS, and many other novel agents with unique mechanisms of action are on the horizon.

During a recent OncLive Peer Exchange®, a panel of hematologic cancer experts shared their insights on the most recent FDA-approved agents for MDS, including luspatercept (Reblozyl) and decitabine/cedazuridine (Inqovi), both of which were approved in 2020. They also examined some novel emerging treatments, including pevonedistat, magrolimab, and venetoclax (Venclexta), all 3 of which have been granted FDA breakthrough therapy designation as MDS treatments for patients with higher-risk disease, although pevonedistat’s future in MDS has become uncertain because it recently missed achieving its primary end point of event-free survival (EFS) in the phase 3 PANTHER trial (NCT03268954).

**LUSPATERCEPT**

Luspatercept is a first-in-class erythroid maturation agent. Impaired erythroid maturation contributes to ineffective erythropoiesis, resulting in low production of red blood cells (RBCs) and anemia. Luspatercept enhances late-stage erythropoiesis by binding several endogenous transforming growth factor-β superfamily ligands, thereby diminishing SMAD2/3 signaling. SMAD2/3 proteins have been found to be constitutively activated and overexpressed in MDS bone marrow precursors.

“The exciting thing about luspatercept is that it was the first drug we got approved for MDS [in over a decade], so that by itself is a milestone for all the people who have worked on this,” Rami Komrokji, MD, said. Luspatercept is approved for the treatment of anemia failing an erythropoiesis-stimulating agent and requiring at least 2 RBC units over 8 weeks in adult patients with very low-risk to intermediate-risk MDS with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis.

The FDA approval of luspatercept was based on data from the double-blind phase 3 MEDALIST trial (NCT02631070), which randomly assigned 229 patients with very
low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts requiring regular RBC transfusions to receive either luspatercept at a dosage of 1.0 mg/kg to 1.75 mg/kg (n = 153) or placebo (n = 76), administered subcutaneously every 3 weeks.11 Transfusion independence for at least 8 weeks was achieved in 38% of the patients in the luspatercept arm vs 13% of those in the placebo arm (P < .001). A significantly higher percentage of patients in the luspatercept arm than in the placebo arm met the secondary end point of transfusion independence for at least 12 weeks (28% vs 8%, respectively, for weeks 1 through 24; 33% vs 12%, respectively, for weeks 1 through 48; P < .001 for both comparisons).11

“The real benefit of transfusion independence was in patients who were not heavily transfusion dependent,” Komrokji said. “Once patients get into the 6 to 8 units every other month, those patients may benefit a little bit in transfusion reduction, but not really transfusion independence. So, in my algorithm now, if patients have had an adequate trial of ESA [erythropoietin-stimulating agents] and we are now moving to the next step, I ask whether they have ring sideroblasts. If they do, I try to introduce luspatercept a little bit earlier, before the patients are heavily transfusion dependent.”

In the MEDALIST trial, the most common luspatercept-associated adverse events (AEs) of any grade included fatigue, diarrhea, asthenia, nausea, and dizziness, with the incidence of AEs decreasing over time. “We have had a couple of patients who had to come off [treatment], but in general it was very well tolerated,” Komrokji said. He emphasized the importance of following the escalating dosing outlined in the package insert for patients who are not RBC transfusion free after 2 consecutive doses (6 weeks) at the recommended 1-mg/kg starting dose.

DECITABINE/CEDAZURIDINE
Decitabine/cedazuridine is a fixed-dose oral combination therapy that pairs a nucleoside metabolic inhibitor (ie, decitabine) with a novel cytidine deaminase inhibitor (ie, cedazuridine).12 It is indicated for adult patients with previously treated or untreated, de novo and secondary MDS with the following French-American-British subtypes: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia (CMML).13 It is also indicated for patients with MDS who fall into intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

FDA approval of decitabine/cedazuridine was based on data from 2 open-label, randomized, crossover trials: the phase 1/2 ASTX727-01-B trial (NCT02103478), which included 80 adult patients with MDS or CMML, and the phase 3 ASTX727-02 trial (NCT03306264), which included 133 adult patients with MDS or CMML.4 “Pharmacokinetically and from a response perspective, it looks like [decitabine/cedazuridine is] the same as decitabine,” Gail J. Roboz, MD, said. She explained that the addition of cedazuridine allows oral dosing by preventing the decitabine from being completely broken down by the gastrointestinal tract and liver, which would limit decitabine’s oral bioavailability.

In the clinical trials, oral decitabine/cedazuridine administered as a 100/35-mg fixed-dose tablet was found to provide equivalent decitabine exposure to intravenous (IV) decitabine 20 mg/m² when both were administered over 5 days.4,11 The decitabine area under the curve (AUC) 5-day geometric mean estimate was 856 from the oral combination and 865 from IV decitabine, resulting in an oral/IV AUC ratio of 98.9%.11 Additionally, clinical responses were consistent with those seen in patients receiving IV decitabine. The complete response (CR) rate for the oral combination was 18% in the 01-B trial and 21% in the 02 trial, with median durations of response of 8.7 months and 7.5 months, respectively.4 Among the patients who were dependent on RBC and/or platelet transfusions at baseline, approximately 50% in both trials became independent of RBC and platelet transfusions during any 56-day postbaseline period, with greater than 60% remaining transfusion independent during any 56-day postbaseline period.

The tolerability of oral decitabine/cedazuridine was consistent with that of IV decitabine.4 The most common AEs and laboratory abnormalities with the oral combination are summarized in the TABLE.4,12

“Oral decitabine is really a major improvement in delivery and I’m prescribing it to my patients, but the message for the community is: You still need to bring those patients in every week and check your counts,” Komrokji said. “The fact that it’s a pill doesn’t mean you see them next month. Bring them back every week as if you are doing IV or subcutaneous hypomethylating agents.”

Azra Raza, MD, agreed, stating, “I’ve treated over 25 patients with it already. I love this oral drug. The problem is in the first few that I started, according to the FDA guidelines, there was tremendous myelosuppression, which I didn’t see ever with decitabine alone. We must remember that. But then once I got used to using this drug, so many of my older patients now, after 5 or 6 months of trial and error, they’re coming once a month [for follow-up]. And that’s huge.”

PEVONEDISTAT
Pevonedistat is a novel investigational
agent being studied for MDS in PANTHER.8 “The mechanism of action is really interesting to me. It’s kind of an upscale upstream proteasome inhibitor in a way. It’s called an NAE inhibitor,” James Foran, MD, said. Pevonedistat inhibits the NEDD8-activating enzyme (NAE), preventing cullin-RING E3 ubiquitin ligases (CRL) substrates from degrading—a process integral to tumor cell growth, proliferation, and survival, as CRL controls the cell cycle, hypoxia signaling, reactive oxygen species clearance, and DNA repair.14,15

At the time of the Peer Exchange, Foran expressed excitement about pevonedistat based on data from a randomized phase 2 trial that showed a signal in some high-risk patients but noted that data from PANTHER had yet to be reported. On September 1, 2021, the drug’s manufacturer Takeda announced these data, indicating that pevonedistat did not achieve predefined statistical significance for its primary end point of EFS.8 The full data set is still being evaluated and the hope is that the trial findings will help guide further research for the development of potential treatment options for patients with MDS, CMML, and low-blast acute myeloid leukemia (AML). PANTHER compared pevonedistat plus the demethylating agent azacitidine with azacitidine alone in these patients.

VENETOCLAX

Venetoclax is a first-in-class agent that selectively binds to and inhibits the B-cell lymphoma-2 (BCL2) protein, which prevents some hematologic cancers from undergoing apoptosis.7 By inhibiting BCL2 protein, venetoclax helps restore the natural apoptosis process. Venetoclax is already approved as a monotherapy for adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma and in combination with azacitidine, decitabine, or low-dose cytarabine for lymphoma and in combination with azacitidine for adult patients with chronic lymphocytic leukemia or small lymphocytic leukemia.

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“Obviously, the [venetoclax] data in AML looks great. It’s changed the practice. I’ll have to say the natural thing in MDS is we follow immediately after AML so it’s already made its way into practice actually, without the data completely supporting it,” Komrokji said. He noted that he has used venetoclax outside of clinical trials for patients with MDS but that he would not recommend this for general oncology practices unless they have “very good infrastructure to support monitoring those patients closely,” because it is an intensive therapy with toxicity concerns, including myelosuppression.

Komrokji said he thinks venetoclax looks especially promising as a transplant preparing regimen in MDS. In one small real-world study of patients with treatment-naïve and relapsed/refractory MDS, venetoclax plus hypomethylating agents showed an overall response rate of 59%, with 63% of responders proceeding to allogeneic stem cell transplantation, a treatment associated with prolonged survival.17

Venetoclax is being studied in multiple clinical trials, including the phase 3 Verona study (NCT04401748), which is recruiting patients and assessing oral venetoclax in combination with IV or subcutaneous azacitidine in adults with newly diagnosed higher-risk MDS (FIGURE).18 A primary outcome measure for the trial is overall survival. “I would encourage everybody listening to this [Peer Exchange], whenever your patients logistically have access to a clinical trial, please send them because there really are trials that are going to change the landscape of MDS,” Komrokji emphasized.

MAGROLIMAB

“Magrolimab is a really interesting drug and it’s the first-in-class macrophage immune checkpoint inhibitor,” Amy DeZern, MD, MHS, explained. “It targets CD47, which is that ‘don’t eat me’ signal that’s actually expressed in a lot of cancers.” Use of magrolimab may be especially promising for patients with MDS who have TP53 mutations, an underserved population with poor outcomes. Most TP53 mutations cause changes to single amino acids in the p53 protein, causing an altered version of the protein to be produced that cannot control cell proliferation and is unable to trigger apoptosis in cells with mutated or damaged DNA, causing DNA damage to accumulate.19

“Some promising data showed that magrolimab might be just as good or even better in [patients with] TP53 [mutations]. It’s not monotherapy; it is combined with azacitidine,” DeZern said, referring to the results of a phase 1b study (NCT03248479) by Sallman and colleagues.20 The study included 39 patients with untreated intermediate-risk to very high-risk MDS and 29 patients with AML deemed unfit for chemotherapy with 27% of patients having TP53 mutation. All patients were treated with magrolimab plus azacitidine.

In RBC-transfusion-dependent patients
with MDS, 58% became transfusion independent. Among the efficacy-evaluable patients with MDS, 30 of 33 (91%) had an objective response, with 42% CRs, 24% marrow CRs (4/8 also with hematologic improvement [HI]), 3% PRs, and 21% HI alone. Additionally, 9% had stable disease. Responses in the MDS arm deepened over time, with a 56% CR rate in patients with at least 6 months of follow-up. Cytogenetic CR was seen in 35% of responders in the MDS arm. The median duration of response was not reached in either arm, including the patients with TP53 mutations, and 91% of patients in the MDS arm were in remission at 6 months. The overall survival estimate at 6 months for patients in the MDS arm was 100%.

Overall, treatment was well tolerated, with a safety profile similar to azacitidine alone. The most common treatment-related AEs included anemia (38%), fatigue (21%), neutropenia (19%), thrombocytopenia (18%), and infusion-related reactions (16%).

“We are hoping to see real extension of life [in people with TP53 mutations],” DeZern said. “I’m not sure it’s going to be specifically for TP53 patients. I think it certainly treats all comers, but I’m hoping it is something that will be in our arsenal in the future that can augment the life of those patients with what is really the worst of the worst higher-risk disease.”

REFERENCES
AGAVE-201 (SNDX-6352-0504/NCT04710576) is a Phase 2, randomized, multicenter study to evaluate the efficacy, safety, and tolerability of 3 dose levels of axatilimab (SNDX-6352) in patients with recurrent or refractory active cGVHD who have received at least 2 lines of systemic therapy.

For more information about the AGAVE-201 clinical trial, including full eligibility criteria and study sites, please visit www.clinicaltrials.gov (NCT04710576) or www.syndax.com/pipeline/sndx-6352-cgvhd.

Contact Syndax directly at clinicaltrials@syndax.com

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