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Genomic Testing Challenges Persist

by ANITA T. SHAFFER

Outcomes for patients who receive targeted therapies have vastly improved compared with historical standards. Despite the advantages molecular panels may provide and guidelines for several tumor types recommending their use, community oncologists face several hurdles when it comes to integrating testing into routine practice in the community practice.
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Content Is King in Oncology Meeting Reporting

AS WE APPROACH THE end of the first half of 2022, all eyes are set on the American Society of Clinical Oncology (ASCO) Annual Meeting. As one of the largest medical oncology meetings gets ready to return in-person, the OncLive® editorial team is gearing up to bring you the biggest news and exclusive interviews with faculty in attendance at the meeting.

It’s been a busy year thus far with practice-changing data coming out of meetings including the American Association for Cancer Research 2022 Annual Meeting, the Society of Gynecologic Oncology 2022 Annual Meeting, and the 2022 ASCO Gastrointestinal and Genitourinary Symposia. Hundreds of articles and exclusive interviews are hosted on OncLive.com highlighting the wealth of information from these events.

A distillation of these data for clinical practice is a key feature of meetings hosted by Physician’s Education Resource® (PER®), LLC throughout the year. For example, this issue of OncologyLive® features coverage of the 15th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies. Expert faculty from across genitourinary cancers gathered in March to evaluate emerging safety and efficacy data from recently reported clinical trials of novel therapeutic strategies and assess their effect on standards of care.

Our coverage features insights from Primo Nery Lara Jr, MD, on the role of risk-stratification for treatment decisions in renal cell carcinoma. Another article highlights the top takeaways from Susan F. Slovin, MD, PhD, who unpacked advances and setbacks with immunotherapy in prostate cancer based on the latest data from the ASCO 2022 Genitourinary Symposium. Finally, cochair of the meeting Leonard G. Gomella, MD, FACS, discussing the growing role of genomic and genetic germline testing in treatment and screening decisions for individuals with prostate cancer.

The conference coverage section of OncologyLive® highlights only a small fraction of the meetings covered throughout the year. In addition to live coverage as the biggest news breaks, OncLive® features interviews with key opinion leaders on how the latest data will affect clinical practice. To stay abreast of the latest updates and insights, please subscribe to OncLive® newsletters at bit.ly/3B6RTsM.

To further provide oncologists with the most up-to-date information, PER® is hard at work planning and executing affiliated symposia, Medical Crossfire® programs, and more, both during and after major meetings. Be sure to visit gotoper.com to register for the virtual or in-person programs hosted during the ASCO Annual Meeting.

As always, thank you for reading.
Mike Hennessy Jr
President and CEO
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We Must Improve Communication With the Public

by MAURIE MARKMAN, MD

THE SCIENTIFIC COMMUNITY HAS BEEN in some ways stunningly ineffective in clearly communicating highly relevant information about the COVID-19 virus and pandemic to the public.

Several factors help explain this discouraging state of affairs, including that baseline satisfactory skills for communicating with the lay public and/or specific training in this area have not been a priority within the scientific establishment. In addition, the rapidly changing scientific evidence associated with multiple components of the pandemic may mandate frequent alterations in public health-related recommendations.

It is not difficult to appreciate how this state of affairs can lead to loss of faith in any government-produced guidelines, leading many to ask: “Do they know what they are doing?” It is much easier for critics to declare a recommendation that disrupts normal life activities (eg, wearing masks, social distancing, business lockdowns) to be without sufficient foundation than it is for the scientifically and evidence-based public health community to provide definitive objectively valid data in its support.

Perhaps one should not have been surprised, considering the status of the national public health community among many members of society, to see actions taken in direct opposition to the formal position and guidance from the CDC.1 Further, potential associations between COVID-19 infections and serious medical events (eg, cardiac dysfunction) may remain in the realm of hypothesis or anecdote for considerable periods of time—potentially years rather than weeks or months—before it is possible to make a formal claim acceptable to the scientific, medical, and public health communities.2 Such is often the nature of objectively valid clinical investigation.

Again, it should not be surprising that those making statements related to vaccine adverse effects or unsubstantiated claims for a COVID-19 therapeutic may sound more authoritative and even more knowledgeable to those in the general public than the cautious and tentative words of a spokesperson representing objective science.

One additional factor needs to be considered: the rapidly expanding role of social media. In a recent commentary in Science, authors Dominique Brossard, PhD, MS, MPS, and Dietram A. Scheufele, PhD, MA, made several thoughtful and crucial observations about the current scientific information landscape, including the following:

• “Since the early days of the internet, the scientific community has had a very spotty track record of harnessing the full potential of online communication tools to reach beyond an audience that already follows science.”

• “The same profit-driven algorithmic tools that bring science-friendly and curious followers to scientists’ Twitter feeds and YouTube channels will increasingly disconnect scientists from the audiences that they need to connect with most urgently.”

• “Social media platforms and their underlying algorithms are designed to outperform the ability of science audiences to sift through rapidly growing information streams and to capitalize on their emotional and cognitive weaknesses in doing so.”

One of the overarching problems, as noted by Holden Thorp, PhD, editor in chief of Science, is that “disagreement

“Agencies developing public health guidelines should make information as simple as possible.”
and outlandish statements result in more engagement,” encouraging movement away from authoritative information to leverage the algorithms used by social media companies.4

Although the issues highlighted here are complex, overcoming existing deficiencies will require substantial effort by the scientific community and its leadership. There are certain strategies that may help, such as national groups working closely together on a consensus before public statements are made in order to avoid the confusion that often has clouded governmental pronouncements related to the COVID-19 pandemic.

In addition, agencies developing public health guidelines should make information as simple as possible. Yes, clinical science can be messy. For example, alternative and competing treatment approaches or drugs may be available for patients, and experts may strongly disagree about optimal strategies based on the availability of high-quality data. But we need to think about the primary care physician, the specialist, or the patients who are not experts and are attempting to understand different approaches to manage even the most common clinical problems.

For example, consider the existing recommendations for cervix cancer screening in the United States. At what age should screening begin? What is the optimal test strategy? What is the effect of prior vaccination, either complete or partial? Several national organizations, such as the American College of Obstetricians and Gynecologists, Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, US Preventive Services Task Force, and the American Cancer Society, have developed their own guidelines, which, although similar, are far from identical.1 Is it really that difficult to come to a consensus regarding a recommendation for screening?

Imagine the very busy primary care clinician, family care physician, pediatrician, generalist obstetrician/gynecologist, or other practitioner responsible for advising patients about such a critically important individual and public health measure. Is it any surprise that results of a recent study comparing data from 2005 to 2019 demonstrated a highly disturbing decrease in the percentage of women aged 21 to 65 years who were up-to-date on screening for cervical cancer?6

The investigators concluded this decline was not because of lack of access or prior human papillomavirus vaccination but because of “lack of knowledge and not receiving recommendations from health care professionals.”6 Remarkable.

Even though cervical cancer screening is one of the most successful public health measures implemented during the past 50 years, the medical, scientific, and public health communities are being told their efforts to deliver simple, clear, and vital information regarding this highly effective approach in cancer prevention is failing. This mess needs to be fixed.

REFERENCES
The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients

Consistent results with or without prior adjuvant chemotherapy

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

*Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.
†Control arm=placebo.
‡Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40) and for patients without adjuvant chemotherapy was HR=0.03 (95% CI: 0.01, 0.15).

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

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

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

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

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

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

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

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

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

**References:**

3. DoFP. REF: 98491. AstraZeneca Pharmaceuticals LP.
4. DoFP. REF: 98525. AstraZeneca Pharmaceuticals LP.
TAGRISSO® (osimertinib) tablets, for oral use
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
TAGRISSO is indicated as an adjuvant therapy to surgery in patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as determined by an FDA-approved test.[see Dosage and Administration (2.1) in the full Prescribing Information].

First-line Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)
TAGRISSO is indicated for the first-line treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as determined by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.[see Dosage and Administration (2.1) in the full Prescribing Information].

Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC
TAGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as determined by an FDA-approved test.[see Dosage and Administration (2.1) in the full Prescribing Information].

Table 1. Recommended Dosage Modifications for TAGRISSO

<table>
<thead>
<tr>
<th>Organelle</th>
<th>Adverse Reaction</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal lining (LD/Liver/Pancreas)</td>
<td>GCQ Interval greater than 600 mm or less than 2 epochs (E)</td>
<td>without TAGRISSO until GCQ Interval is less than 600 mm or recovery to baseline if baseline GCQ is greater than or equal to 481 mm, then resume at 40 mg dose</td>
</tr>
<tr>
<td>Symptomatic congestive heart failure (ICH)</td>
<td>QTc Interval greater than 500 ms or less than 2 epochs (E)</td>
<td>without TAGRISSO until QTc Interval is less than 500 ms or recovery to baseline if baseline QTc is greater than or equal to 481 ms, then resume at 40 mg dose</td>
</tr>
</tbody>
</table>

Note: All Grades represents the percentage of patients. Grade 3 or 4 represents the percentage of patients with grades 3 or 4. TABLES 1 AND 2 SHOW THE ADVERSE REACTIONS REPORTED TO BE AT LEAST 2% IN PATIENTS TREATED WITH TAGRISSO OR PLACEBO.

QTc Interval Prolongation
Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 8% were found to have a QTc >500 ms, and 3% of patients had an increase from baseline QTc >480 ms.[see Clinical Pharmacology (12.2) in the full Prescribing Information].

No QTc-related arrhythmias were reported. Clinical trials of TAGRISSO did not enroll patients with baseline QTc >470 ms. Conduct periodic monitoring with ECGs and electrolytes in patients with congestive heart failure (CHF), congenital heart block, or prolonged QTc intervals, or those with other conditions predisposing to QTc prolongation to make decisions regarding the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with symptoms of life-threatening arrhythmia.[see Dosage and Administration (2.4) in the full Prescribing Information].

Cardiomyopathy
Across clinical trials, cardiomyopathy defined as cardiac failure, cardiac conduction defects, heart failure with preserved ejection fraction occurred in 2% of the 1497 TAGRISSO treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) >50 percentage points from baseline and >30% LVEF drop occurred in 3.1% of patients who had baseline and at least one follow-up LVEF assessment. In the ADJURA study, 1.5% (5/325) of patients treated with TAGRISSO experienced LVEF decreases greater than or equal to 10% points from baseline.[see Clinical Pharmacology (12.2) in the full Prescribing Information].

Contact dermatitis, drug eruption, eczema, folliculitis, nephrotoxicity, photosensitivity reaction, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) therapy.[see Dosage and Administration (2.1) in the full Prescribing Information].

Adverse Reactions

Gastrointestinal Disorders
Nausea* 47 2.4 29 0.3
Diarrhea 37 2.0 3.0 0.3
Anorexia 13 0.3 7 0.3
Skin Disorders
Rash* 46 0.6 19 0.3
Nail toxicity 37 0.9 3.0 0.3
Dry skin 19 0.3 3.0 0.3
Pruritus 13 0.2 6 0.2
Respiratory, Thoracic and Mediastinal Disorders
Cough 19 0.0 19 0.3
Musculoskeletal and Connective Tissue Disorders
Arthralgia 18 0.3 25 0.3
Infection and Infestation Disorders
Nasopharyngitis 14 0.1 10 0.0
Upper respiratory tract infection 13 0.6 15 0.0
Upper respiratory and sinus infections 13 0.6 15 0.0
Urinary tract infection* 10 0.3 7 0.3
Lower urinary tract infection 10 0.3 7 0.3
General and Administrative Site Disorders
Fatigue 18 0.3 9 0.3
Nervous System Disorders
Dizziness* 10 0.0 9 0.0
Metabolism and Nutrition Disorders
Decreased appetite 13 0.8 3.0 0.3
Hyperglycemia 10 0.3 10 0.3
* All events were grade 3.
** Includes diabetes mellitus, diabetes mellitus, gestational diabetes mellitus, diabetes mellitus.
§ Includes diabetes mellitus, diabetes mellitus, gestational diabetes mellitus, diabetes mellitus.
¶ Includes diabetes mellitus, diabetes mellitus, gestational diabetes mellitus, diabetes mellitus.
$ Includes dry skin, pruritus, pruritus, pruritus.
Expected adverse reactions observed in the clinical trials of a drug can be directly compared to those in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Adjuvant and Neoplastic Disorders section reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials (ADAURA (n=337), FLAURA (n=279), and AURA3 (n=279)), and one dose-finding study, AURORA (n=173) [see Warnings and Precautions (5.1) in the full Prescribing Information]. Among 1479 patients who received TAGRISSO, 81% were exposed for 6 months or longer and 50% were exposed for greater than or equal to 1 year of follow-up.

The most common laboratory abnormalities were ≥30% of patients who received TAGRISSO were increased hemoglobin (3.0%), increased alkaline phosphatase (2.7%), increased total bilirubin (2.6%), decreased triglycerides (2.4%), increased AST (2.3%), increased ALT (2.3%), increased gamma-glutamyl transferase (2.2%), increased total protein (2.2%), decreased platelets (2.1%), increased sodium (2.1%), increased bilirubin (2.0%), increased creatinine (1.9%), increased albumin (1.8%), increased cholesterol (1.8%), decreased MCV (1.8%), decreased MCH (1.8%), decreased MCHC (1.8%), decreased WBC (1.8%), increased red blood cell distribution width (1.8%), increased platelets (1.8%), increased prothrombin time (1.8%), increased hemoglobin A1c (1.8%), increased lymphocytes (1.8%), increased monocytes (1.8%), increased neutrophils (1.8%), increased eosinophils (1.8%), increased neutrophils (1.8%), increased lymphocytes (1.8%), increased monocytes (1.8%), increased neutrophils (1.8%).

The most commonly laboratory abnormalities in ≥30% of patients who received TAGRISSO were increased hemoglobin (3.0%), increased alkaline phosphatase (2.7%), increased total bilirubin (2.6%), decreased triglycerides (2.4%), increased AST (2.3%), increased ALT (2.3%), increased gamma-glutamyl transferase (2.2%), increased total protein (2.2%), decreased platelets (2.1%), increased sodium (2.1%), increased bilirubin (2.0%), increased creatinine (1.9%), increased albumin (1.8%), increased cholesterol (1.8%), decreased MCV (1.8%), decreased MCH (1.8%), decreased MCHC (1.8%), decreased WBC (1.8%), increased red blood cell distribution width (1.8%), increased platelets (1.8%), increased prothrombin time (1.8%), increased hemoglobin A1c (1.8%), increased lymphocytes (1.8%), increased monocytes (1.8%), increased neutrophils (1.8%), increased eosinophils (1.8%), increased neutrophils (1.8%), increased lymphocytes (1.8%), increased monocytes (1.8%), increased neutrophils (1.8%).
Clinical relevant adverse reactions in FLAURA in <10% of patients receiving TAGRISSO were alopecia (7%), epistaxis (6%), interstitial lung disease (3.9%), urticaria (2.2%), and dry skin (3.2%). QTc interval prolongation represents the incidence of patients who had a QTcF interval as assessed by ECG (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was QTcF prolongation (1.4%).

Drug Interactions

Effect of Other Drugs on Osimertinib

TAGRISSO is a strong CYP3A inducer. Decreased CYP3AINDUCED drugs, such as warfarin, HIV protease inhibitors, and some antibiotics, may have decreased efficacy. Co-administering TAGRISSO with a strong CYP3A4 inducer at usual doses is not recommended due to the risk of reduced omeprazole exposure.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increased TAGRISSO doses may be necessary when co-administering a strong CYP3A4 inducer. Consider adjusting the dose of TAGRISSO to maintain appropriate exposure based on clinical benefit and tolerability.

Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp) substrate could increase the exposure of such drugs. Avoid concomitant administration of such drugs, conduct periodic ECG monitoring (see [see Use in Specific Populations (8.1) in the full Prescribing Information]).

SPECIFIC USES IN POPULATIONS

Pregnancy

Consent

Females and Males of Reproductive Potential

Use in Specific Populations

Geriatric Use

The effects on female fertility showed a trend toward reversibility. It is not known if TAGRISSO reduces female fertility. Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO.

The following laboratory abnormalities were observed in baseline in 22% of patients in FLAURA.

Laboratory Abnormality

Table 2. Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in FLAURA

Table 3. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA

Adverse Reaction

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

Adverse Reaction

Table 5. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

Laboratory Abnormality

Table 6. Summary of Common Adverse Reactions and Laboratory Abnormalities Which Occurred in ≥5% of Patients Treated With TAGRISSO

Adverse Reaction

Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

Laboratory Abnormality

Table 8. Common Adverse Reactions Occurring in ≥10% of Patients Treated With TAGRISSO in AURA3

Adverse Reaction

Table 9. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3

Adverse Reaction

Table 10. Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in AURA3

Laboratory Abnormality

Table 11. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

Laboratory Abnormality

Table 12. Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in AURA3

Laboratory Abnormality

Table 13. Common Adverse Reactions Occurring in ≥10% of Patients Treated With TAGRISSO in AURA3

Adverse Reaction

Table 14. Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in AURA3

Laboratory Abnormality

Table 15. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

Laboratory Abnormality
**DEEP DIVE**

**Study Aims to Increase CRC Screening Rates in Rural Areas**

Jennifer Weiss, MD, and colleagues have initiated a 4-year study to improve and sustain screening rates for colorectal cancer (CRC) in rural clinics. The aim is to survey more than 200 rural primary care clinics in the upper Midwest to identify high-performing clinics—defined as having successfully screened at least 80% of eligible patients—to identify common best practices. Weiss, who is affiliated with the University of Wisconsin-Madison Carbone Cancer Center, hypothesized that distance from providers who perform colonoscopies may be an issue that patients in rural settings face and that reasonable alternatives such as at-home stool tests may be a solution for this population. This is also a more affordable option than a colonoscopy, she explained.

> TO WATCH, VISIT [bit.ly/3jiCy0a](https://bit.ly/3jiCy0a).

**INSIDE THE PRACTICE**

**New Device Improves Excision of Axillary Lymph Nodes**

For patients with breast cancer that has spread to the axillary lymph nodes, the use of a new reflector device technology in the early neoadjuvant chemotherapy setting can help more accurately pinpoint cancerous nodes for resection, according to Leslie L. Montgomery, MD, and Tara M. Balija, MD, of Hackensack University Medical Center in New Jersey. A study conducted by the institution showed that in 22 of the 57 patients who had the reflector device placed 8 weeks or more before surgery, or in the early- to mid-neoadjuvant chemotherapy setting, efficacy in identifying positive axillary lymph nodes increased to 100%. Conversely, among patients who had the device placed within 8 weeks of surgery, the efficacy was just 79.2% ($P = .02$).


**WELL-BEING CHECKUP**

**ECOG-ACRIN Works to Address Disparities in Cancer Care**

Edith P. Mitchell, MD, MACP, FCPP, FRCS, of Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, is at the forefront of the efforts driving change in health disparities in cancer care. As cochair of the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) Health Equity Committee, Mitchell works with her colleagues to increase the accrual of Black patients to ECOG-ACRIN clinical trials, support up-and-coming Black providers who are in or plan to work in cancer medicine, foster advocacy groups in underserved communities, and provide bias training to practitioners. The goal is to have a comprehensive group of individuals involved and working together, Mitchell explained.


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Towards Harmonization of Pathology and Oncology Standards

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**KEY TOPICS TO BE DISCUSSED**
- Gastrointestinal oncology
- Genitourinary oncology
- Breast oncology
- Lung oncology

**CO-CHAIRS**
- **Balazs Halmos, MD, MS**
  Professor of Clinical Medicine
  Director, Thoracic/Head and Neck Oncology
  Director, Clinical Cancer Genomics
  Albert Einstein College of Medicine/Montefiore Medical Center
  Bronx, NY
- **Lynette M. Sholl, MD**
  Associate Professor, Pathology
  Harvard Medical School
  Associate Pathologist, Pathology
  Brigham and Women’s Hospital
  Boston, MA

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Second-Line Axi-Cel Expands Treatment Options for LBCL

The FDA has approved axicabtagene ciloleucel (axi-cel; Yescarta) for the second-line treatment of adult patients with large B-cell lymphoma (LBCL) who are refractory to first-line chemoimmunotherapy or who have relapsed within 12 months of first-line chemoimmunotherapy. The regulatory approval is supported by data from the phase 3 ZUMA-7 trial (NCT03391466).

At a median follow-up of 24.9 months, the estimated median event-free survival (EFS) with the chimeric antigen receptor T-cell therapy was 8.3 months (n = 180; 95% CI, 4.5-15.8) vs 2.0 months (95% CI, 1.6-2.8) with standard of care (SOC; n = 179; HR, 0.4; 95% CI, 0.31-0.51; P < .0001). The estimated 18-month EFS rates in the investigative and control arms were 41.5% (95% CI, 34.2%-48.6%) and 17.0% (95% CI, 11.8%-23.0%), respectively.

In the investigative arm, the objective response rate (ORR) was 83% (95% CI, 77%-88%), including a 65% (95% CI, 58%-72%) complete remission (CR) rate and an 18% (95% CI, 13%-25%) partial remission (PR) rate. In the control arm, the ORR was 50% (95% CI, 43%-58%), with a 32% (95% CI, 26%-40%) CR rate and an 18% (95% CI, 13%-24%) PR rate.

Notably, axi-cel has a boxed warning for cytokine release syndrome and neurologic toxicities. For more on the axi-cel approval, see PAGE 20.

TO READ MORE, VISIT bit.ly/38EnqYZ.

Pembrolizumab Label Is Expanded to Include Select Advanced Endometrial Cancer

The FDA has approved pembrolizumab (Keytruda) for use as a single agent in the treatment of patients with prostate-specific membrane antigen (PSMA)–positive metastatic castration-resistant prostate cancer (CRPC) who have previously received an androgen receptor–pathway inhibitor and taxane-based chemotherapy, Lomacmetaz—a radioactive diagnostic agent for positron emission tomography of PSMA-positive lesions—was simultaneously given the go-ahead.

The approval was supported by data from the phase 3 VISION trial (NCT03511664), which showed that when the targeted radioligand therapy was combined with standard of care (SOC), it resulted in a 38% reduction in the risk of death (n = 551) vs SOC alone (n = 280). The median overall survival in the investigative arm was 15.3 months vs 11.3 months in the control arm (HR, 0.62; 95% CI, 0.52-0.74; P < .001).

Data on radiographic progression-free survival was significant, but interpretation of the magnitude was limited due to a high degree of censoring from early drop out in the control arm.

Further, the overall response rates were 30% (95% CI, 25%-35%) with addition of the investigative agent vs 2% (95% CI, 0%-6%) with SOC alone.

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

Pemetrexed Label Is Expanded to Include Select Advanced Endometrial Cancer

The FDA has approved pemetrexed (Alimta) for treatment of patients with advanced endometrial carcinoma that is microsatellite instability–high or mismatch repair–deficient and who experienced disease progression following systemic therapy in any setting and are not candidates for curative surgery or radiation.

The regulatory decision is based on findings from cohorts D and K of the phase 2 KEYNOTE-158 trial (NCT02628067). At a median follow-up of 16.0 months (range, 0.5-62.1), the immunotherapy elicited an objective response rate of 46% (95% CI, 35%-65%) among 41 treated patients, with a complete response rate of 12% and a partial response rate of 33%.

Notably, 68% of patients experienced responses that lasted 12 months or longer, and 44% experienced responses that lasted 24 months or longer. The median duration of response with the agent in these patients had not been reached.

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

FDA Sets Plan for Decision on Futibatinib for FGFR2+ Advanced Cholangiocarcinoma

The FDA has granted priority review to a new drug application (NDA) seeking the approval of futibatinib (TAS-120) for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions. Under the Prescription Drug User Fee Act, the regulatory agency will decide on the NDA by September 30, 2022.

The application is based on results from the phase 2b FOENIX-CCA2 trial (NCT02052778), in which the agent was found to elicit an objective response rate (ORR) among 103 patients of 41.7% per independent central review, with a median duration of response of 9.7 months. Notably, 72% of responders continued to respond for 6 months or more. Moreover, the ORR benefit with futibatinib proved to be consistent across all patient subsets analyzed, including those who were aged 65 years and older (65.2%) and those who previously received 2 or more treatments (38.7%). Additionally, futibatinib resulted in a disease control rate of 82.5% and a median progression-free survival of 9.0 months. The median overall survival (OS) with the agent was 21.7 months, and the 12-month OS rate was 72%.

TO READ MORE, VISIT bit.ly/3jedKWT.
Indication
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Safety Information

Warnings and Precautions

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

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
RAISING THE STANDARD
FOR SURVIVAL

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*1

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash1

Important Safety Information

Warnings and Precautions

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

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

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

Adverse Reactions

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

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

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.
If diarrhea occurs, administer antidiarrheal treatment as indicated to exclude other causes of diarrhea. Based on the severity of hepatotoxicity, interrupt dose, then reduce or permanently discontinue TUKYSA. Based on the severity of hepatotoxicity, interrupt dose, then reduce or permanently discontinue TUKYSA.

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

**Drug Interactions**

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

**Use in Specific Populations**

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

Please see Brief Summary of Prescribing Information on adjacent pages.

**References:**


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**In combination with trastuzumab + capecitabine**

**TUKYSA reduced the risk of disease progression or death**

**PRIMARY ENDPOINT**

**PFS**

46% reduction in the risk of disease progression or death

- HR = 0.54 (95% CI: 0.42–0.71); P < 0.00001
- Median PFS: 7.8 months (95% CI: 7.5–9.6) in the TUKYSA arm vs 5.6 months (95% CI: 4.2–7.1) in the control arm

---

**EXPLORATORY ANALYSIS**

**PFS AT 12 MONTHS**

- ~3x as many patients were progression-free

<table>
<thead>
<tr>
<th>TUKYSA ARM (33.1%; 95% CI: 26.6–39.7)</th>
<th>CONTROL ARM (12.3%; 95% CI: 6.0–20.9)</th>
</tr>
</thead>
</table>

---

**Lab Abnormalities**

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

**Use in Specific Populations**

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

Please see Brief Summary of Prescribing Information on adjacent pages.

**References:**

**TUKYSA® (tucatinib) tablets, for oral use**

Brief summary of Prescribing Information (PI). See full PI. Rx Only

**INDICATIONS AND USAGE**

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

**DOSEAGE AND ADMINISTRATION**

**Recommended Dosage**

The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity. Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time. When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

**Dosage Modifications for Adverse Reactions**

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

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

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

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

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

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea¹</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

**Hepatotoxicity²**

| Grade 2 bilirubin (>1.5 to 3 × ULN) | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level. |
| Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> 3 to 10 × ULN) | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level. |
| Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN) | Permanently discontinue TUKYSA. |
| ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN | Permanently discontinue TUKYSA. |

Other adverse reactions³

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

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase
3. Other adverse reactions include, but are not limited to, those listed in the table above.

**WARNINGS AND PRECAUTIONS**

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

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

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

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

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

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Stomatitis¹</td>
<td></td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>43.0</td>
<td>0.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Rash²</td>
<td></td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

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

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

**CONTRAINDICATIONS**

None.
with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

**USE IN SPECIFIC POPULATIONS**

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59</td>
<td>3.3</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>47</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased AST</td>
<td>59</td>
<td>8</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>40</td>
<td>0.8</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Decreased alkaline phosphate</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NC-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NC-CTCAE v.5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v.4.03.

1. Increases in serum creatinine were ≤ 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Table 5: Abnormalities (≥1%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

1. Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, ulceration, glossodynia, tongue blistering, lip blister, oral dysaesthesia, tongue ulceration, and aphthous ulcer
2. Rash includes rash maculo-papular, rash, dermatitis annoneum, erythema, rash macular, rash papular, rash purulential, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis
3. Hepatotoxicity includes hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury
4. Anemia includes anemia, hemoglobin decreased, and normocytic anemia
5. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function
6. Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

**REFERENCES**

**Drug Interactions**

**Effects of Other Drugs on TUKYSA**

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

**Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP3A inducer increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

**Effects of TUKYSA on Other Drugs**

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary:** TUKYSA is used in combination with trastuzumab and capecitabine.

**Females and Males of Reproductive Potential**

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine.

**Geriatric Use:** In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (8%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

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

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

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AXICABTAGENE CILOLEUCEL (YESCARTA)

Second-Line Axi-Cel Offers a “Practice-Changing” Indication for LBCL
by JACKIE COLLINS

BASED ON DATA FROM the phase 3 ZUMA-7 trial (NCT03391466), the FDA has approved axicabtagene ciloleucel (axi-cel; Yescarta) for the second-line treatment of adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or who experience relapse within 12 months of first-line chemoimmunotherapy.¹

Event-free survival (EFS) rates with this second-line chimeric antigen receptor (CAR) T-cell therapy recorded in ZUMA-7 were efficacious over second-line standard-of-care (SOC) treatment in the form of investigator-chosen platinum-based chemoimmunotherapy. Distinctively, at a median follow-up of 24.9 months, the estimated median EFS with single-infusion axi-cel (n = 180) was 8.3 months (95% CI, 4.5-15.8) vs 2.0 months (95% CI, 1.6-2.8) with SOC treatment (n = 179; HR, 0.40; 95% CI, 0.31-0.51; P < .0001). Moreover, the estimated 18-month EFS rates in the investigative and control arms were 41.5% (95% CI, 34.2%-48.6%) and 17.0% (95% CI, 11.8%-23.0%), respectively.

Additional data showed that axi-cel improved objective response rate (ORR) over SOC. In the investigative arm, the ORR was 83% (95% CI, 77%-88%), including a 65% (95% CI, 58%-72%) complete remission (CR) rate and an 18% (95% CI, 13%-25%) partial remission (PR) rate. In the control arm, the ORR was 50% (95% CI, 43%-58%), with a 32% (95% CI, 26%-40%) CR rate and an 18% (95% CI, 13%-24%) PR rate.²

Notably, this CAR T-cell therapy has a boxed warning for cytokine release syndrome (CRS) and neurologic toxicities.

In an interview with OncologyLive®, Lori A. Leslie, MD, reviewed how the approval of this novel designation may impact or enhance current practice patterns for this patient population. Leslie is director of the Indolent Lymphoma and Chronic Lymphocytic Leukemia Research Programs at John Theurer Cancer Center of Hackensack Meridian Health and an assistant professor at Hackensack Meridian School of Medicine in New Jersey.

What is the significance of this designation?
The approval of axi-cel for second-line LBCL is exciting for our patients, particularly our high-risk patients who have...either primary refractory disease or [relapse] early after their frontline therapy.

We know historically that these patients do not do as well with our prior SOC—which is salvage chemotherapy and autologous stem cell transplantation [ASCT]—mostly because these patients are at high risk of having chemotherapy-refractory disease. Therefore, ASCT is something that is hard to do in this patient population if they are not responding to chemotherapy.

A CAR T-cell therapy approval for these patients gives them the opportunity to go straight to an immunotherapy-based option. We are reharvesting the power of their immune systems’ T cells to attack the lymphoma and helping spare these patients from that extra step of salvage chemotherapy when we know that they have a low chance of response. That is exciting for our patients, and it is practice changing.

What effect does this approval have on current practice patterns?
The current treatment landscape for [patients with] LBCL [who] have relapsed—regardless of when the patient has relapsed—is to [usually] do [platinum-based] salvage chemotherapy followed by an ASCT for patients who are fit enough to do so. We know that certain patients with LBCL have a high risk of being refractory to chemotherapy. To be a candidate for ASCT, you must have chemotherapy-sensitive disease. Understanding now that we have an approval for CAR T-cell therapy helps us know to spare salvage chemotherapy for patients who are at high risk of not responding. Currently, the treatment landscape is to use CAR T-cell therapy in the third-line setting. Moving it into the second-line setting gives our patients an opportunity to avoid some of the added toxicities of salvage therapy when we know their chance of benefiting from that is small.

It is also important because, unlike ASCT, CAR T-cell therapy can be used in a wider variety of patients; there is no upper age limit cutoff for most studies. We are familiar with CAR T-cell therapy since its initial approval in 2017; we have been using it in a more expanded patient population, including older patients and patients with well-controlled comorbid conditions. These are patients who would not be candidates for ASCT.

What AEs should clinicians be aware of when prescribing axi-cel?
There are 2 main groups of toxicities that are relatively unique to this type of therapy and to similar types of immune-mediated therapies. The first is CRS, and that is an overactivation of the immune system. This is treated usually while the patients are in the hospital and is typically an event that happens early after administration of CAR T-cell therapy. [Initial] treatment is to give tocilizumab (Actemra), which is an anti-IL-6 antibody, and then, in more severe cases, to give corticosteroids.

The other group of toxicities involves neurologic events. Unlike CRS, these are a little more unpredictable. They also typically happen early on, within the first week, of getting the CAR T-cell therapy [and] can [include] a wide variety of symptoms; it can be as simple as some minor handwriting change or mild confusion, or patients can get much more notable neurologic [adverse] effects and even become obtunded. [Symptoms are] monitored closely while patients are in the hospital post CAR T-cell therapy, and the treatment is initiation of steroids.

With our current treatment algorithms, we [can] intervene earlier, knowing that intervention with tocilizumab and steroids does not impair the efficacy of the CAR T cells, and we are able to prevent these higher grades of AEs. In most patients, however, it is important to know that they must be monitored at the treatment site for these specific toxicities as part of the [Risk Evaluation and Mitigation Strategy] program.

What is the next step for CAR T-cell therapy research?
CAR T-cell therapy is expanding across hematologic malignancies and solid tumors. Axi-cel and the currently available CAR T-cell products for third-line, and now second-line, LBCL are all targeting CD19. CAR T-cell therapy is moving earlier in the treatment landscape, not only for LBCL as early as frontline, but also for some of the other lymphomas, [such as] indolent lymphomas, follicular lymphoma, and mantle cell lymphoma.

Moving forward, we will see a similar trend that we have seen in LBCL, with CAR T[ cell therapy] being available earlier in the treatment landscape. We have approvals in multiple myeloma and research ongoing in [chronic lymphocytic leukemia].

Expanding into solid tumors, investigators are looking at other targets rather than CD19 for CAR T-cell therapy, [and] there is an emerging group of protocols and data that [will] hopefully [have us] talking about CAR T[ cell therapy] for [most] cancers.

REFERENCES
FDA approval—April 1, 2022
The FDA grants approval to axicabtagene ciloleucel (axi-cel; Yescarta) for the treatment of adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoinmunotherapy or who experience relapse within 12 months of first-line chemoinmunotherapy.

Mechanism of action
• Axi-cel is a CD19-directed genetically modified autologous T-cell immunotherapy that binds to CD19-expressing cancer cells and normal B cells.

How supplied
• Infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% dimethyl sulfoxide and 2.5% albumin.

Recommended dose
• 2 × 10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2 × 10^8 CAR-positive viable T cells.

Company: Kite Pharma, Inc

PIVOTAL CLINICAL TRIAL
ZUMA-7 (NCT03391466) was a randomized, open-label, multicenter trial evaluating axi-cel in adult patients with relapsed or refractory LBCL after first-line chemoinmunotherapy that included rituximab (Rituxan) and anthracycline.

EFFECTIVENESS IN THE ZUMA-7 TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Axi-cel (n = 180)</th>
<th>SOC (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events, n (%)</td>
<td>108 (60)</td>
<td>144 (80)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>8.3 (4.5-15.8)</td>
<td>2.0 (1.6-2.8)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>18-month rate (95% CI)</td>
<td>41.5% (34.2%-48.6%)</td>
<td>17.0% (11.8%-23.0%)</td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (95% CI)</td>
<td>8.3% (77%-88%)</td>
<td>50% (43%-58%)</td>
</tr>
<tr>
<td>CR rate (95% CI)</td>
<td>95% CI, 23%-42%; P &lt; .0001</td>
<td></td>
</tr>
<tr>
<td>PR rate (95% CI)</td>
<td>65% (58%-72%)</td>
<td>32% (26%-40%)</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events, n (%)</td>
<td>93 (52)</td>
<td>81 (45)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>14.9 (7.2-NE)</td>
<td>5.0 (3.4-8.5)</td>
</tr>
</tbody>
</table>

CR, complete remission; EFS, event-free survival; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial remission; SOC, standard of care.

*Following fludarabine and cyclophosphamide lymphodepleting chemotherapy.
*Consisting of 2 or 3 cycles of chemoinmunotherapy followed by high-dose therapy and autologous hematopoietic stem cell transplantation.

BOXED WARNING

• Cytokine release syndrome
• Neurologic toxicities

WARNINGs AND PRECAUTIONs

• Hypersensitivity
• Serious infections
• Prolonged cytopenias
• Hypogammaglobulinemia
• Secondary malignancies
• Effects on ability to drive and use machines

COMMONLY REPORTED ADVERSE EFFECTS IN THE ZUMA-7 TRIAL

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Any grade</th>
<th>Grade 3 or higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>93%</td>
<td>9%</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>92%</td>
<td>7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52%</td>
<td>7%</td>
</tr>
</tbody>
</table>

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Patients who underwent leukapheresis</th>
<th>178</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who were treated with axi-cel</td>
<td>170</td>
</tr>
</tbody>
</table>

| Patients who received bridging corticosteroid therapy | 8 |
| Patients who were not treated following leukapheresis* | 67% |

*Primarily due to progressive disease, serious adverse events, or death.

Median time from leukapheresis to product therapy, days (range)

Median time from leukapheresis to axi-cel infusion, days (range)

Median dose of axi-cel, CAR-positive viable T cells/kg (range)

2.0 × 10^6 (1.0 × 10^6 to 2.1 × 10^6)

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor.

Median time to onset of CRS

3 DAYS

Median duration of CRS

7 DAYS

CRS, cytokine release syndrome.

REFERENCES

Drug Spotlight

Nivolumab Plus Chemotherapy Moves Into Neoadjuvant Setting in NSCLC

by KYLE DOHERTY

ADULT PATIENTS WITH RESECTABLE non–small cell lung cancer (NSCLC) gained a new neoadjuvant treatment option with the March 4, 2022, FDA approval of the anti–PD-1 antibody, nivolumab (Opdivo), in combination with platinum-doublet chemotherapy.1 The approval was based on data from the phase 3 CheckMate 816 trial (NCT02998528).

Results from the study showed that patients treated with nivolumab plus chemotherapy (n = 179) achieved a median event-free survival (EFS) of 31.6 months (95% CI, 30.2–not reached) compared with 20.8 months (95% CI, 14.0–26.7) among the 179 patients who received chemotherapy alone (HR, 0.63; 97.38% CI, 0.45–0.87; P<.005). The pathological complete response (pCR) rate was also much greater in the group that received the combination compared with the chemotherapy arm, 24.0% (95% CI, 18.0%–31.0%) vs 2.2% (95% CI, 0.6%–5.6%), respectively (odds ratio, 13.94; 99% CI, 3.49–55.75; P<.001).2

In an interview with OncologyLive®, Mark Awad, MD, PhD, discussed how the approval opens the door for this regimen to become a backbone for future treatment strategies. Awad is the clinical director of the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute and an associate professor of medicine at Harvard Medical School in Boston, Massachusetts.

What was the clinical rationale for evaluating nivolumab plus chemotherapy in this patient population and disease setting?

We know that in early-stage [NSCLC], even after surgical resection, chemotherapy, or standard radiation therapies, many of these patients have a high risk of recurrence after definitive therapy or surgical resection. There is a huge clinical need to develop improved curative therapies for patients with early-stage NSCLC. The rationale for this study was to bring the successes we’ve seen with immunotherapy in stage IV NSCLC, unresectable stage III NSCLC, and many other tumor types, and apply it to the early-stage disease setting to see [whether] we can increase the cure rate.

What did you find noteworthy about the efficacy data that led to this approval?

What was extremely notable was that when you add immunotherapy to standard platinum-doublet chemotherapy, the pCR rate was significantly higher. It was [approximately] 10 times higher vs using standard chemotherapy alone. Among patients in this trial who [received] chemotherapy before surgery, approximately 2% had a pCR at the time of surgery. But in patients who had chemotherapy plus nivolumab, the pCR rate was approximately 24%. That is quite meaningful, as a primary or surrogate end point.

What we don’t have a lot of information about yet is how well that pCR rate translates into the next end point, which we typically talk about: disease-free survival. Does that mean there is going to be less recurrences? Does that then translate to improvements in overall survival or decreases in deaths from lung cancer?

We saw data presented [in 2021] about the potential surrogate end point of pCR rate, [and] it does seem that [benefit] translated into an improvement in EFS. Hopefully, in the long run, that will also translate to improved overall survival. It is a practice-changing trial and practice-changing approval.

What new directions in research does this approval influence in NSCLC?

There are [several] outstanding questions, because the trial did enroll patients with different [disease] stages. [This included] stage II and stage III, [as well as] patients with or without lymph node involvement or lymph node metastasis. It also enrolled patients regardless of PD-L1 expression level.

The questions for us are: Are there certain subgroups that benefited more so than others with the addition of immunotherapy to chemotherapy? Does this approach and regimen work regardless of the subgroups of stages [and/or] the subgroups of patients with different PD-L1 levels? Does it work as well in [individuals] who have never smoked vs [those] who have smoked?

We still need to see the details of the trials to understand [whether] this regimen can be used across the board in all-comers with resectable lung cancer, [whether] there are subgroups that have an even greater benefit, and [whether there are] other individuals [for whom] this regimen may not be as effective. Hopefully, this will change the treatment paradigm for resectable lung cancer in that there will be more multidisciplinary discussions between medical oncologists, thoracic surgeons, and radiation oncologists to discuss the best overall treatment approach for patients with potentially resectable lung cancer. I believe [the results of this trial will] lead to incorporating more use of immunotherapy with chemotherapy prior to surgery.

What adverse effects (AEs) should clinicians be aware of when prescribing this regimen?

From the data that have been presented, it seems [AEs are] reasonably manageable and this is a well-tolerated regimen. But the immunotherapy can cause rare but potentially serious immune-related AEs. There can be rare complications such as pneumonitis, colitis, dermatitis, endocrine disorders, or other rare toxicities that can be serious for patients. As we do for patients with metastatic lung cancer, where we use immunotherapy or for other cancers, we [must] diligently monitor for the development of these AEs.

What does the future hold for nivolumab plus chemotherapy in NSCLC and beyond?

Prior to this approval, we already had an approval [based on results of the] IMpower010 [NCT02486718] study, which [evaluated] adjuvant atezolizumab [Tecentriq]. One question is: Should we be using immunotherapy before surgery, after surgery, or both? There are some trials that are looking at that question of this sandwich approach of giving immunotherapy both before and after surgery.

As I mentioned, [there are] outstanding questions about subgroups. Of course, predicting toxicity is an important question that we don’t know how to [answer] yet, with immunotherapy and [in] any cancer. Then there are many patients who still do not benefit from immunotherapy or chemotherapy.

There are many additional approaches trying to use novel immunotherapies, targeted therapies, or other novel therapeutics in patients with metastatic lung cancer, as well as many other tumor types. There are already several trials being launched that are combining novel agents with these standard regimens. I believe this will become a new backbone regimen, from which we can hopefully build upon and develop additional improved therapies.

REFERENCES
FDA approval—March 4, 2022
FDA grants approval to nivolumab (Opdivo) plus platinum-doublet chemotherapy for adult patients with resectable non–small cell lung cancer (NSCLC) in the neoadjuvant setting.

Mechanism of action
• Nivolumab is a human immunoglobulin G4 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
• 40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL, and 240 mg/24 mL solution in a single-dose vial

Dosing
• 360 mg plus platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles

Company: Bristol Myers Squibb

PIVOTAL CLINICAL TRIAL
CheckMate 816 (NCT02998528) was a randomized, open-label trial of patients with resectable, histologically confirmed stage IB, II, or IIIA NSCLC and measurable disease, regardless of PD-L1 status. Investigators evaluated the addition of nivolumab to platinum-based chemotherapy vs chemotherapy alone followed by resection.

EFFICACY RESULTS IN THE CHECKMATE 816 TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab plus chemotherapy (n = 179)</th>
<th>Chemotherapy (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median EFS, months (95% CI)</td>
<td>31.6 (30.2–NR)</td>
<td>20.8 (14.0–26.7)</td>
</tr>
<tr>
<td>pCR rate (95% CI)</td>
<td>24% (18%-31%)</td>
<td>2.2% (0.6%-5.6%)</td>
</tr>
<tr>
<td>Major pathological response</td>
<td>36.9%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Patients who went to surgery</td>
<td>83.2%</td>
<td>75.4%</td>
</tr>
</tbody>
</table>

EFS, event-free survival; NR, not reached; OR, odds ratio; pCR, pathological complete response.

WARNINGS AND PRECAUTIONS
• Immune-mediated reactions
• Infusion-related reactions
• Complications of allogeneic hematopoietic stem cell transplantation
• Embryo-fetal toxicity

COMMONLY REPORTED ADVERSE EFFECTS IN THE CHECKMATE 816 TRIAL

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Nivolumab plus chemotherapy (n = 176)</th>
<th>Chemotherapy (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hematologic adverse effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Nivolumab plus chemotherapy (n = 176)</th>
<th>Chemotherapy (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>63%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58%</td>
<td>22%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>53%</td>
<td>5%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>38%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

REFERENCES
Indications
Retevmo is a kinase inhibitor indicated for the treatment of:
- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information
Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension: Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-medullary thyroid cancer (non-MTC)),* and advanced or metastatic RET-mutant MTC1

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
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<tbody>
<tr>
<td><strong>85% ORR</strong>†</td>
<td><strong>64% ORR</strong>†</td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> not yet reached</td>
<td><strong>Median DoR</strong> was 17.5 months</td>
</tr>
<tr>
<td>(95% CI: 12, NE)</td>
<td>(95% CI: 12, NE)</td>
</tr>
<tr>
<td>median follow-up: 7.4 months†</td>
<td>median follow-up: 12.1 months†</td>
</tr>
</tbody>
</table>

**Metastatic RET Fusion-Positive NSCLC**

<table>
<thead>
<tr>
<th>Treatment naive (n=8)</th>
<th>Previously treated (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100% ORR</strong>†</td>
<td><strong>79% ORR</strong>†</td>
</tr>
<tr>
<td>(95% CI: 65, 100)</td>
<td>(95% CI: 54, 94)</td>
</tr>
<tr>
<td>12.5% CR + 88% PR</td>
<td>5.3% CR + 74% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> not yet reached</td>
<td><strong>Median DoR</strong> was 18.4 months</td>
</tr>
<tr>
<td>(95% CI: NE, NE)</td>
<td>(95% CI: 76, NE)</td>
</tr>
<tr>
<td>median follow-up: 8.8 months†</td>
<td>median follow-up: 17.5 months†</td>
</tr>
</tbody>
</table>

**Metastatic RET Fusion-Positive Thyroid Cancer (Non-MTC)**

<table>
<thead>
<tr>
<th>Systemic therapy naive (n=8)</th>
<th>Previously treated (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>73% ORR</strong>†</td>
<td><strong>69% ORR</strong>†</td>
</tr>
<tr>
<td>(95% CI: 62, 82)</td>
<td>(95% CI: 55, 81)</td>
</tr>
<tr>
<td>11% CR + 61% PR</td>
<td>9% CR + 60% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> was 22.0 months†</td>
<td><strong>Median DoR</strong> not yet reached</td>
</tr>
<tr>
<td>(95% CI: NE, NE)</td>
<td>(95% CI: 19.1, NE)</td>
</tr>
<tr>
<td>median follow-up: 7.8 months†</td>
<td>median follow-up: 14.1 months†</td>
</tr>
</tbody>
</table>

Find RET. Find results on Retevmo.com.

**Adverse Reactions and Laboratory Abnormalities**

- The most common adverse reactions, including laboratory abnormalities, (>25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction (in >2% of patients) was pneumonia. Fatality adverse reactions occurred in 3% of patients; fatality adverse reactions which occurred in >1% patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%)

- Dose reductions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥3% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue

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*Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.

†Patients previously treated with platinum-based chemotherapy and with measurable CNS lesions at baseline according to IRC assessment.

‡Patients in this cohort received a prior systemic therapy including sorafenib, lenvatinib, or both other than RAI.

§§ Patients with advanced or metastatic RET-fusion-positive thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.

** Patients previously treated with platinum-based chemotherapy and those without prior systemic therapy were enrolled in the following cohorts: systemic therapy-naive patients (n=39)†† and previously treated (n=19)†† patients with advanced or metastatic RET-fusion-positive thyroid cancer (non-MTC), and treatment-naive (n=88) and previously treated (n=55)†† patients with advanced or metastatic RET-mutant MTC. Major efficacy outcomes were ORR and DoR. In phase II, the dose for Retevmo was 160 mg PO BID.1,4,5,8 OPR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v1.1.1 All patients reviewed by an IRC.1,1
Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTc interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diabetes, Correct hypocalcemia, hypomagnesemia and hypokalemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, hemorrhagic events can occur with Retevmo. Onset of hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at a maternal dose of 1 mg/kg/day (approximately equal to the observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose.

There are no data on the presence of selpercatinib or its metabolites in human milk or on 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 Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3–4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were hypertension (18%), prolonged QT interval (16%), diarrhea (9.4%), dyspnea (5.2%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥2% of patients) was pneumonia.

Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.

References:
RETEVMO® (selpercatinib) capsules, for oral use

INITIAL U.S. APPROVAL: 2020

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE
RETEVMO (selpercatinib) is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic RET-fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion-positive thyroid cancer who require systemic therapy due to radioactive iodine-refractory (if radioactive iodine is appropriate).

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 0.6% of patients, including Grade 3 or 4 events in 0% and increased ALT occurred in 49% of patients, including Grade 3 or 4 events in 9%. The median time to onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 33% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity.

QT Interval Prolongation
RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTc interval to >60 ms was measured in 6% of patients and an increase in the QTc interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based on risk factors including diabetes. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong or moderate CYP3A inhibitors or drugs known to prolong QTc interval.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETEVMO. Grade 3 hemorrhagic events occurred in 2.9% of patients treated with RETEVMO, including 0.4% patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, transeptal catheter site hemorrhage, and hemoptysis.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.1%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included rashes, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

RISK OF IMPAIRED WOUND HEALING
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on data from animal reproduction studies and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats and rabbits resulted in fetal abnormalities. Avoid exposure to RETEVMO during pregnancy.

In females of reproductive potential and males with female partners of reproductive potential to use effective contraception.

RETEVMO™ (selpercatinib) capsules, for oral use

Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Dry Mouth</td>
<td>39</td>
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<tr>
<td>Diarrhea</td>
<td>37</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Vomiting</td>
<td>15</td>
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<tr>
<td>Vascular</td>
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<tr>
<td>Hypertension</td>
<td>36</td>
</tr>
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</table>

SE HCP BS 08/MAY/2020

RETEVMO™ (selpercatinib) capsules, for oral use

SE HCP BS 09/MAY/2020
Table 1: Adverse Reactions (>15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>2</td>
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<td>Edema</td>
<td>33</td>
<td>0.3</td>
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<tr>
<td><strong>Skin</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>0.7</td>
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<tr>
<td><strong>Respiratory</strong></td>
<td></td>
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<tr>
<td>Headache</td>
<td>23</td>
<td>1.4</td>
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<td><strong>Investigations</strong></td>
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<tr>
<td>Cough</td>
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<tr>
<td>Diarrhea</td>
<td>16</td>
<td>2.3</td>
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<tr>
<td><strong>Laboratory Abnormalities</strong></td>
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<tr>
<td>Decreased WBC</td>
<td>51</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Increased WBC</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>44</td>
<td>2.2</td>
<td></td>
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<tr>
<td>Increased platelet count</td>
<td>38</td>
<td>0.7</td>
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<tr>
<td>Decreased calcium</td>
<td>41</td>
<td>3.6</td>
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<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.0</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>2.3</td>
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<tr>
<td>Increased total cholesterol</td>
<td>31</td>
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<tr>
<td>Decreased sodium</td>
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<td>2</td>
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<tr>
<td>Increased magnesium</td>
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<td>0.6</td>
<td></td>
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<tr>
<td>Increased potassium</td>
<td>24</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**DRUG INTERACTIONS**

**Effects of Other Drugs on RETEVMO**

**Acid-Reducing Agents**

Concomitant use of RETEVMO with acid-reducing agents decreases selipetublin plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antisecrets with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally acting antacid).

**Strong and Moderate CYP3A Inhibitors**

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selipetublin plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QTc interval with ECGs more frequently.

**Strong and Moderate CYP3A Inducers**

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selipetublin plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

**Effects of RETEVMO on Other Drugs**

CYP2C8 and CYP3A Substrates

RETUVMO is an in vitro inhibitor of CYP3A and a weak CYP2C8 inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow the recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

**Drugs that Prolong QT Interval**

RETUVMO is associated with QTc interval prolongation. Monitor the QTc interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selipetublin to pregnant rats during the period of organogenesis resulted in embryopathy and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

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

**Data**

**Animal Data**

Selipetublin administration to pregnant rats during the period of organogenesis at oral doses ≥100 mg/kg (approximately 3 to 10 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6% of females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

**Lactation**

**Risk Summary**

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

Table 2: Select Laboratory Abnormalities (%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO (n=702)</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
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</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
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</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
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</tr>
<tr>
<td>Decreased calcium</td>
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<tr>
<td>Increased alkaline phosphatase</td>
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<tr>
<td>Increased total cholesterol</td>
<td>31</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
<td>1.2</td>
<td></td>
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<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0</td>
<td></td>
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<tr>
<td>Decreased glucose</td>
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<td></td>
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<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6</td>
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</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.
Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing

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

Contraception

Females

Advising female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Males

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

Infertility

RETEVMO may impair fertility in females and males of reproductive potential.

Pediatric Use

The safety and effectiveness of RETEVMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications.

Animal Toxicity Data

In 4-week general toxicology studies in rats, animals showed signs of physical hypertrophy and tooth dysplasia at doses resulting in exposures ≥ approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physical thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rates in both the 4- and 15-week toxicology studies had macrophage and tooth dysplasia at the high dose levels (≥1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Geriatric Use

Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance (CrCl) ≥30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease.

Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

Rx only.

Additional information can be found at www.retevmo.com.
ALTHOUGH MOLECULAR BIOMARKERS are becoming increasingly relevant in cancer care, community oncologists confront a plethora of challenges in translating research findings into practice. Structural changes in payment systems and decision-support tools are among the most critical needs that must be addressed to broaden the use of genomic testing in clinical practice, according to experts.

During the past 5 years, findings from real-world analyses indicate that patients with a range of tumor types are not being tested for biomarkers recommended in guidelines, leading to suboptimal use of targeted therapies. Investigators have lamented “pervasive undertesting” for tumor-specific biomarkers and inherited cancer risk. They have cited a complex web of factors that are impeding the uptake of genomic testing, such as gaps in knowledge among providers and support for interpreting test results, shortcomings in tissue samples (particularly in lung cancer), a lack of access to tests, and reimbursement challenges.

Overcoming these hurdles will require greater support for oncologists in day-to-day practice so they can obtain molecular testing for their patients and decipher results in an easily digestible format, Howard L. McLeod, PharmD, FASCO, FCCP, said. McLeod is the executive clinical director of precision health at Intermountain Healthcare, a network of hospitals and medical groups based in Utah.

“I remember when PET [positron emission tomography] scans first came out, even when the data were present, there was a reluctance to use it because [oncologists] felt like no one had their back—it was nuclear medicine [specialists] who interpreted it and they didn’t really know those folks,” McLeod said. “Then radiology started interpreting it. Now you see PET scan, or PET/CT, being ordered for many patients because someone had the oncologist’s back.

“That’s what needs to happen in the molecular arena to really make this routine,” McLeod added. “It’s not fair that oncologists have to keep up on more things than they’re able to and, just because you’re in a community setting, you should not be punished by not having a good backup for applying these technologies.”

Molecular testing can be challenging even in tumor types such as non-small cell lung cancer (NSCLC), in which somatic alterations in at least 7 genes have been identified as being clinically relevant to the therapy selection for patients with advanced disease. Community-based practices must send out tissue specimens for analysis, resulting in turnaround times that could delay the start of therapy, noted Tracey L. Evans, MD, director of thoracic oncology research at Lankenau Institute for Medical Research in Wynnewood, Pennsylvania, and codirector of the thoracic oncology program at the affiliated Main Line Health system.

“There’s a real sense of urgency for patients, especially those with metastatic NSCLC, who can be very symptomatic. You don’t always feel like you have the time to wait to get that genomic testing back, even though it’s critically important,” Evans said in an interview.

The adoption of reflex testing, in which a pathologist automatically orders the required tests based on clinical pathways, would help expand the use of molecular profiling in NSCLC and perhaps other tumor types, Evans said. “This is something that is routinely done in breast cancer, where all patients are tested for HER2, ER [estrogen receptor], and PR [progesterone receptor],” she said.

However, reimbursement barriers for lining up molecular testing can be significant. In addition to obtaining prior authorization, Evans noted, oncologists may also have to contend with the “14-day rule” enforced by the Centers for Medicare & Medicaid Services. Under that policy,
Genomic Testing

physicians may have to wait 14 days after a patient is discharged from the hospital to order certain laboratory tests, a delay that could be problematic for patients with NSCLC who were hospitalized because of emergent symptoms.4

“There’s a myriad of challenges that go into this, and I’m sympathetic to physicians who have a difficult time doing it,” Evans said.

RECOGNIZING A NEED FOR CLARITY

Strategies for leveraging advances in tumor biology are becoming more important considering the growing number of FDA-approved anticancer therapies for molecularly defined populations, experts have observed. Although many alterations occur at low frequency, research findings have increased understanding of the frequency of mutations, particularly in the most prevalent cancers, which amplifies the potential clinical utility of genomic testing (TABLE 1).

However, there is a lack of clarity when it comes to choosing and ordering genomic sequencing tests and in interpreting results, according to an American Society of Clinical Oncology (ASCO) expert panel. In April, the panel published a provisional clinical opinion with recommendations for somatic genomic testing in patients with advanced or metastatic solid tumors.5

For these patients, genomic sequencing should be conducted on tumors for which genomic alterations have been identified as biomarkers to guide the use of approved therapies, the panel said. If more than 1 biomarker is associated with therapy for a given malignancy, tumors should be tested with multigene panel assays, defined as next-generation sequencing (NGS) tests that analyze a defined list of at least 50 genes.

Additional clinical scenarios involving tumor-agnostic biomarkers such as tumor mutational burden (TMB), mismatch repair deficiency (dMMR), or NTRK fusions also create a strong rationale for conducting genomic testing on all patients with advanced or metastatic solid tumors, the panel said. “For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments,” the ASCO authors noted.

DOCUMENTING GAPS IN TESTING

Although such broad-based strategies may offer the best option for ensuring that all patients who are candidates for molecularly selected therapies receive testing, findings from several studies suggest that the oncology field is far from reaching that goal.

Only 26.7% of patients with localized or metastatic gastrointestinal stromal tumors (GISTs) received testing for KIT mutations, according to an analysis of information extracted from the Surveillance Epidemiology and End Results (SEER) database from 2010 to 2015.6 Knowledge of KIT mutational status is an important predictive and prognostic biomarker for the treatment of GISTs.6

In a retrospective review of electronic health data from 2013 through 2017 for patients with metastatic colon cancer, investigators found that less than 50% of patients had guideline-recommended testing for RAS alterations, BRAF mutations, and microsatellite instability/dMMR.7

More recent results show an increased uptake of molecular testing among patients in some clinical settings but not in others. Additionally, testing rates continue to lag guideline recommendations.

In NSCLC, the proportion of patients with newly diagnosed advanced disease who were tested for EGFR mutations before the initiation of first-line therapy increased from 45.2% to 56.6% from January 1, 2015, through November 30, 2020, according to an analysis of information for 22,726 patients in the Flatiron Health database presented during the 2021 ASCO Quality Care Symposium.9

In another study, the use of NGS testing increased significantly from 33% to 45% (P < .0001) of patients with metastatic NSCLC initiating first-line systemic therapy between April 1, 2018, and March 31, 2020, at community oncology practices in The US Oncology Network. The retrospective review was conducted by MYLUNG Consortium, a collaboration between The US Oncology Network, pharmaceutical companies, and patient advocacy groups.10

Among 3474 patients, 90% were tested for at least 1 of 5 biomarkers but only 46% were tested for all of them. Testing rates were 70% for EGFR mutations and ALK translocations, 68% for ROS1 rearrangements, 53% for BRAF mutations, and 83% for PD-L1 protein expression.10 “Our real-world study showed that most patients with metastatic non–small cell lung cancer had at least 1 biomarker test result available prior to initiation of first-line therapy,” Makenzi Evangelist, MD, a medical oncologist and hematologist at New York Oncology Hematology in Albany and Clifton Park, New York, said in presenting the results at the 2021 ASCO Annual Meeting. “However, only approximately 50% of patients had all 5 tests available prior to first-line therapy. NGS testing was low but increased over time. This may provide a better opportunity for comprehensive biomarker testing.”

In contrast to the improvements observed in lung cancer testing, there is a wide chasm between guideline recommendations and clinical practice concerning germline genetic testing in ovarian cancer. Patients diagnosed with ovarian, fallopian tube, or primary peritoneal cancer should receive genetic risk evaluation as well as germline and somatic mutation testing, according to National Comprehensive Cancer Network (NCCN) guidelines.11 For genetic risk assessment, the NCCN recommends testing for BRCA1/2 mutations and other high-penetration cancer susceptibility genes for patients with a history of ovarian cancer.11

However, only 34.3% of patients diagnosed with ovarian cancer in California or Georgia from 2013 to 2017 (N = 14,689) received multigene panel testing, according to an examination of SEER data reported in the Journal of Clinical Oncology in February 2021. Investigators were dismayed to find that although the use of multigene assays increased compared with testing only for BRCA1/2 mutations, the overall uptake of genetic testing increased by only approximately 3% from 2013 to 2014 levels.12 “There is urgent need to further define the patient, clinician, and health care system

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Gene alteration and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≥5% to 10% frequency</strong></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>PIK3CA* (9.9%), BRCA1 drivers (5.7%)</td>
</tr>
<tr>
<td>Salivary gland cancer</td>
<td>PIK3CA* (8.7%)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>RET drivers (8.1%), RET fusions (5.1%)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>BRAF V600 (7.6%)</td>
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<tr>
<td>Esophageal cancer</td>
<td>PIK3CA* (7.8%)</td>
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<tr>
<td>Cholangiocarcinoma</td>
<td>FGFR2 fusions (7.3%)</td>
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<td>ERBB2 amplification (5.4%)</td>
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<tr>
<td>NSCLC</td>
<td>PIK3CA* (5.2%)</td>
</tr>
<tr>
<td><strong>10% to 50% frequency</strong></td>
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<tr>
<td>Breast cancer</td>
<td>ERBB2 amplification (10.4%)</td>
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<tr>
<td>Cervical cancer</td>
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<td>IDH1 drivers (14.5%)</td>
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</tr>
<tr>
<td>NSCLC</td>
<td>EGFR drivers (26.9%), KRAS G12C (11.3%)</td>
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<td><strong>&gt;50% frequency</strong></td>
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<td>GIST</td>
<td>KiT drivers (78.9%)</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumor; NSCLC, non–small cell lung cancer.

*Driver mutations.
Genomic Testing

factors that limit testing of patients with ovarian cancer and to develop interventions that surmount these barriers, Allison W. Kurian, MD, MSc, and colleagues wrote.

In another study, investigators analyzed germline BRCA (gBRCA) testing patterns among 3603 women treated for ovarian cancer between 2008 and 2018 using claims data from a large national commercial insurer. During the 10-year period, only 33.9% of patients received gBRCA testing. The data show that testing rates were lower for women 65 years and older compared with those younger than 50 years (adjusted difference, −20.8%; 95% CI, −25.8% to −16.4%). There also was a difference in testing according to practice setting, with a lower rate (32.5%) in community practices compared with academic centers (36.2%) and National Cancer Institute centers (39.8%).

When viewed on a year-by-year basis, the proportion of patients tested increased from 14.7% in 2008 to 46.4% in 2018. The median time from diagnosis to germline BRCA testing decreased from 280.0 days in 2008 to 72.5 days in 2018.

Nevertheless, the data show that gBRCA testing remains underutilized despite well-established guidelines recommending universal testing for women with ovarian cancer, investigators noted.

MOVING TOWARD COMPREHENSIVE PROFILING

Some cancer centers are incorporating comprehensive genomic profiling (CGP) into routine practice, such as Intermountain Healthcare, which operates in Utah, Idaho, Nevada, and other Western states. McLeod said all patients with metastatic disease undergo 3 types of analysis: somatic tumor testing, germline testing for heritable cancers, and germline pharmacogenomics testing. Whereas testing for somatic and germline aberrations has dominated attention in the field, the importance of pharmacogenomics in identifying toxicity risks from anticancer therapy is being increasingly recognized.

The somatic testing analyzes approximately 600 genes in DNA and RNA extracted from the tumor and, like the other assays, was developed in house, enabling greater control over turnaround times, McLeod said. “We have the expertise for not only interpreting the molecular piece, but also for doing a molecular tumor board with medical interpretation,” he said. “Our oncologist can quickly see the results and act on them. Many places do the molecular tumor and the molecular pathology piece, and give you a nice report, but the oncologists don’t really have the medical backing that they need. That’s something that’s really overlooked as we’re getting into this precision medicine era.”

Moving forward, some oncology thought leaders expect CGP to become standard practice across tumor types. In December 2017, the FDA approved the FoundationOne CDx genomic test, the first such assay for commercial use.

The oncology field is at “an inflection point,” Bruce A. Feinberg, DO, said during an American Journal of Managed Care Peer Exchange program in December 2021. Feinberg is vice president and chief medical officer at Cardinal Health Specialty Solutions.

“We’re just 4 years from the approval of the first comprehensive genomic profile, which was approved by the FDA as a test for patients with solid-tumor cancer,” Feinberg said. “After 4 years, we may be at the point where comprehensive genetic profiling is no longer the last thing you do when you’ve exhausted all standard of care. Rather, it has become the first thing you do before you initiate any systemic therapy in a patient with advanced cancer.”

For that to happen, oncologists will need decision-support tools that help identify appropriate testing that could then be conducted reflexively, said Kenna R. Mills Shaw, PhD, who participated in the Peer Exchange program. Shaw is executive director of the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy at The University of Texas MD Anderson Cancer Center in Houston. This information can be incorporated into electronic health programs.

“The more that we can put into these electronic health records to provide clinicians with what would be essentially the best practice alert kind of language would help us all do better,” Shaw said in an interview. “[Our systems need to] tweak that balance between notifying a clinician so they don’t have alert fatigue while making sure that [alerts] that truly can benefit patient care and outcomes are taken care of.”

At the same time, Shaw noted that charges continue to be a barrier to more widespread adoption of CGP. The “$1000 genome” has become emblematic of the plummeting costs of sequencing, but Shaw noted that the often-quoted price point refers to a research environment. In clinical practice, CGP can result in charges ranging from $5000 to $10,000 when all expenses are considered, including charges for a high-quality NGS test, a molecularly trained pathologist, and the decision-support team, Shaw said.

Coverage and reimbursement for the cost of NGS testing alone is highly variable, according to findings from a study of medical database claims reported during the 2021 ASCO Annual Meeting. The average allowed amounts ranged from $1269 to $2058 per test for NGS testing conducted during the study period (2016-2019). The average allowed amounts varied from $438 to $3700 per test for NGS-derived tests that included TMB and from $1722 to $2249 per test for hereditary cancers.

In NSCLC, broader use of CGP could be achieved for a modest increase in costs per patient, according to recent study findings. Investigators analyzed direct and associated costs using data that were inflation adjusted to 2018 dollars (Table 2) and incorporated the information into a model they developed for a hypothetical health plan. They concluded that CGP for all patients with advanced NSCLC would expand the number of patients who receive CGP testing and improve outcomes at an additional cost of only $205 per patient.

Ultimately, changes are needed in reimbursement procedures for oncologists to use CGP more extensively, Evans said. Oncologists need “federal payment schemes that recognize the importance of this and are consistent with this, so you don’t have to jump through so many hoops to do something that’s the right thing for the patient,” she said.

“Broadening the utilization is good for patient care and for research,” Evans said. “The downside, of course, is the expense. Health care is already very, very expensive. But I do think of

### TABLE 2. Testing Costs in NSCLC Model

<table>
<thead>
<tr>
<th>Test/procedure</th>
<th>Costa</th>
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<tbody>
<tr>
<td>CGP tissue-based test</td>
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<tr>
<td>CGP conventional liquid test</td>
<td>$3500.00</td>
</tr>
<tr>
<td>Non-CGP tissue-based test</td>
<td>$598.15</td>
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<tr>
<td>Non-CGP conventional liquid test</td>
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<tr>
<td>Fine-needle biopsy</td>
<td>$157.32</td>
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<tr>
<td>Open biopsy</td>
<td>$866.04</td>
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<tr>
<td>Bronchoscopy</td>
<td>$371.66</td>
</tr>
<tr>
<td>Costs associated with liquid testing</td>
<td>$180.72</td>
</tr>
</tbody>
</table>

CGP, comprehensive genomic profiling; NSCLC, non-small cell lung cancer.

*Costs were inflation adjusted to 2018 US dollars based on data from Centers for Medicare & Medicaid Services, published literature, and national inpatient sample data.
the things that we spend money on, this is definitely up there in importance.”

REFERENCES

Thank you for your nominations for the 2022 Giants of Cancer Care® program.

The newest class of Giants will be announced this Spring and will be honored at an Awards Ceremony on June 2, 2022 in Chicago, IL.
Navigating Frontline RCC Treatment Paths Relies on Risk Stratification

by AUDREY STERNBERG

PATIENTS WHO RECEIVE A diagnosis of renal cell carcinoma (RCC) are afforded a variety of treatment options. For those with low-volume indolent disease, active surveillance or cytoreductive nephrectomy may be suitable. Meanwhile, treatment with immun-oncology (IO) agents or tyrosine kinase inhibitors (TKIs) may afford better outcomes for those with favorable-risk disease. Appropriate decision-making depends on risk stratification at the time of diagnosis, according to Primo Nery Lara Jr, MD.

In a presentation during the New York GU™: 15th Annual Interdisciplinary Prostate Cancer Congress® and Other GU Malignancies, Lara, who is director of the University of California Davis (UC Davis) Comprehensive Cancer Center as well as Codman-Radke Endowed Chair in Cancer Research and executive associate dean for Cancer Programs at UC Davis Health in Sacramento, provided an overview of the treatment landscape for patients with metastatic RCC.

Key to developing treatment pathways that involve risk stratification according to International Metastatic RCC Database Consortium (IMDC) criteria is to leverage a multidisciplinary tumor board. “The [first] question that the tumor board tackles is whether an individual with metastatic RCC is a candidate for active surveillance,” Lara said. “From that point, several options are available including cytoreduction and combination immunotherapy-based therapy, which is the standard of care for most patients.”

IO ELIGIBILITY: CHOOSING THE RIGHT TREATMENT PATH

With numerous approved combination regimens, including dual IO therapies and IO/TKI combinations, Lara noted that strategies for choosing between regimens goes beyond eligibility and is contingent on risk stratification. “The standard of care in 2022 for metastatic kidney cancer is immunotherapy-based combination therapy,” he said. “Most of these patients should be considered for combination therapies, and there are several combinations that we would offer depending on their risk group.”

If a patient is deemed eligible for an IO-based combination, those with favorable-risk, intermediate-risk, and poor-risk disease have several options available. These include pembrolizumab (Keytruda) in combination with either axitinib (Inlyta) or lenvatinib (Lenvima), nivolumab (Opdivo) plus cabozantinib (Cabometyx), or avelumab (Bavencio) plus axitinib. For those with intermediate- or poor-risk disease, Lara noted that the immunotherapy doublet of nivolumab plus ipilimumab (Yervoy) is the preferred treatment option, pointing out that the combination does not improve outcomes over sunitinib (Sutent) alone for those with favorable-risk disease.

Four-year follow-up data from the phase 3 CheckMate 214 trial (NCT02231749), which led to the approval of nivolumab plus ipilimumab in patients with frontline metastatic RCC, show the advantage of the combination vs sunitinib in terms of OS for the intention-to-treat population (HR, 0.69; 95% CI, 0.59-0.81) and the intermediate/poor-risk subgroup (HR, 0.65; 95% CI, 0.54-0.78). Patients with favorable-risk disease failed to derive an OS benefit (HR, 0.93; 0.62-1.40).

“[This combination] would be great for intermediate- and poor-risk disease, [but] not so much for favorable risk where it was no better than sunitinib,” Lara said.

Most of the benefit with pembrolizumab/axitinib in the phase 3 KEYNOTE-426 trial (NCT02853331) was isolated to patients with intermediate- or poor-risk disease, Lara noted, despite the combination being recommended for all-risk groups. Updated data at the 42-month follow-up showed sustained OS benefit of the combination (HR, 0.73; 95% CI, 0.60-0.88; P < .001) vs sunitinib in the intention-to-treat population. The benefit was more prominent in the progression-free survival (PFS) analysis, which showed a median PFS of 15.7 months.
In terms of the other recommended therapies, Lara highlighted the advantage of the IO combinations vs single-agent TKI for patients with all-risk disease who are eligible for this treatment pathway. In data from the phase 3 CheckMate 9ER trial (NCT03141177), which supported the approval of cabozantinib and nivolumab in this setting, Lara spotlighted OS results that showed a 40% reduction in the risk of death with the combination vs sunitinib (HR, 0.60; 98.89% CI, 0.40-0.89; P = .0010).

Finally, the phase 3 CLEAR trial (NCT02811861) showed an advantage of lenvatinib plus pembrolizumab vs sunitinib in terms of PFS (HR, 0.39; 95% CI, 0.25-0.59; P < .001) and OS (HR, 0.66; 95% CI, 0.49-0.88; P = .005).

Comparing CLEAR results with those of the previously reviewed trials, Lara said the “results superficially seem to be better if you look at the complete response rate, the median PFS, and [OS]. But you must note that this trial had the lowest percentage of poor-risk patients [vs other pivotal trials reviewed], which will drive a lot of the results of these trials.”

### SINGLE-AGENT SOLUTIONS

For patients who undergo risk stratification and are not eligible for IO therapy, TKIs including sunitinib or pazopanib (Votrient) are preferred treatment options for those with favorable-risk disease. OS outcomes for patients with favorable-risk disease showed a median survival time of 37 months with sunitinib vs 9.4 months among those with poor-risk disease.

"Those who have active autoimmune disease should probably not risk [treatment with] a checkpoint inhibitor. Those with a history of solid organ transplantation and those on supraphysiologic corticosteroids are not your best candidates, or those with illnesses that require chronic immune suppressive therapy," Lara said. “Sometimes there will be a patient who will have a personal preference [to avoid intravenous] therapy or who doesn’t want to go to your clinic because it is too far to drive; they’re not eligible for immunotherapy for those practical reasons.”

In patients with bone-only metastases, cabozantinib monotherapy may be preferable based on results of the phase 2 CABOSUN trial (NCT02496208), which showed a PFS advantage vs sunitinib in the indicated patient subset (0.54; 95% CI, 0.31-0.95). Similarly, Lara said he would use single-agent cabozantinib for patients with non-clear cell papillary RCC and perhaps for those with favorable-risk disease.

“Favorable-risk patients treated with pembrolizumab plus axitinib didn’t seem to benefit from that doublet, so maybe those patients ought to get a VEGFR TKI and then reserved immunotherapy for later,” Lara said.

Conversely, some patients may only be suitable for treatment with single-agent immunotherapy. “For those who are ineligible for or refuse to receive a VEGFR TKI-containing combination, or those patients who [want to avoid] ipilimumab toxicities, single-agent checkpoint inhibitors are reasonable,” he explained. However, he noted that this should be limited to few patients as single-agent high-dose IL-2 and mTOR inhibitors represent 2 treatment options that have little justification for use in an era of more active, life-prolonging therapies.

### SURVEILLANCE VS NEPHRECTOMY

Other branches of the decision tree for patients with metastatic RCC include active surveillance and cytoreduction for patients with favorable-risk disease.

“There is a subset of patients with advanced kidney cancer for whom you could watch [and wait] until such time comes when you do need to treat them with systemic therapies that have adverse effects. The question of who is a candidate for active surveillance is hard to answer because this is a bedside, gut decision," Lara said.

Lara reviewed data from a phase 2 prospective trial of 52 patients that showed surveillance could be a viable treatment option for certain patients with metastatic RCC.8 The median time to treatment initiation was 14.9 months (95% CI, 10.6-25.0) overall, with shortened surveillance associated with adverse risk factors (P = .0403) and higher numbers of metastatic disease sites (P = .0414).

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**FIGURE. Risk-Stratification Treatment Schema for Patients With Newly Diagnosed Clear Cell Metastatic RCC**

![Risk-Stratification Treatment Schema for Patients With Newly Diagnosed Clear Cell Metastatic RCC](image)

- **Active surveillance** (low volume, indolent disease)
- **IO-based combination**
- **INTERMEDIATE OR POOR RISK**
  - Nivolumab/cabozantinib
  - Pembrolizumab/axitinib
- **FAVORABLE RISK**
  - Sunitinib, pazopanib
- **SELECTED PATIENTS**
  - Pembrolizumab
  - Nivolumab
- **NEW YORK GU**

**TABLE.**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAVORABLE RISK</td>
<td>Sunitinib, pazopanib</td>
</tr>
<tr>
<td>INTERMEDIATE OR POOR RISK</td>
<td>Pembrolizumab, Nivolumab</td>
</tr>
<tr>
<td>ALL RISK GROUPS</td>
<td>Pembrolizumab/axitinib, Nivolumab/cabozantinib, Pembrolizumab/lenvatinib, Avelumab/axitinib</td>
</tr>
<tr>
<td>IO</td>
<td>Immunooncology, mRCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitor</td>
</tr>
</tbody>
</table>

---

(95% CI, 13.6-20.2) with the combination vs 11.1 months (95% CI, 8.9-12.5) with sunitinib (HR, 0.68; 95% CI, 0.58-0.80; P < .001).

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Vol. 23 | No. 9 | MAY 2022 35
For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD
WITH A BOLD APPROACH

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

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

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

Learn more at BLENREPHCP.com
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

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

**Keratopathy:** Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 5% were in follow-up, and 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 14% of patients. 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 18%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

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

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

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

**ADVERSE REACTIONS**

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

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (21%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3%), 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 all Prescribing Information, including BOXED WARNING, on the following pages.
Changes in visual acuity may be associated with difficulty for driving and reading. BLENREP causes changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)]. Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

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

1 INDICATIONS AND USAGE
BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication is approved under accelerated approval based on response [see Clinical Studies (14) of full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity
Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 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% of patients recovered to Grade 0 or lower after median follow-up of 6.2 months. Of the 61% who had keratopathy, 56% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

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

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

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

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

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

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

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

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratopathy</td>
<td>71</td>
<td>44</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>53</td>
<td>28</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td><strong>General disorders and administration site complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

Decreased visual acuity was determined upon eye examination.

Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

Dry eyes included dry eye, ocular discomfort, and eye pruritus.

Fatigue included fatigue and asthenia.

Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

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

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

Gastrointestinal Disorders: Vomiting.

Infections: Pneumonia.

Investigations: Albuminuria.

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-blih, 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-blih 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-blih. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

(continued on next page)
8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR <15 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)].
The use of such panels is first informed by a patient’s family history, said Gomez. He emphasized to urologists that asking about an individual’s history of inherited prostate cancer should be augmented by any history of breast and ovarian cancer, melanoma, and Lynch syndrome.
After information concerning family history has been gathered, a genetic counselor can be brought in to discuss testing options, result types, cancer risks, insurance complications, and reproductive implications. This enables the patient to make an informed decision to proceed with genetic testing or not.

"Looking for genetic risk has become baked into our management of prostate cancer today," Gomella said. "Germline and somatic testing are complementary. One does not replace the other. They should both be considered in the management of many patients with prostate cancer." Gomella presented practice guideline recommendations that included key guidance from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors, the NCCN, and the Philadelphia Prostate Cancer Consensus 2017, which are outlined in the FIGURE.

When it comes to determining whether to have patients undergo a biopsy for prostate cancer, a number of methods are available. Among these are prostate-specific antigen (PSA) kinetics, the Prostate Health Index score, OPKO 4Kscore Test, Prostarix, Select MDx, ExoDx Prostate Test, MyProstateScore, a PCA3 test, MRI, and ultrasound. The Prompt Prostate Genetic Score, germline testing, and online calculators are also included.

"[Using] whatever test you're comfortable with is the most important," Gomella said. "At Jefferson Health, we rotate different tests to give our residents exposure to the different potential assays that are available." In terms of whether to perform a repeat biopsy, Gomella cited the ConfirmMDx, Mitomic Prostate Test, MyProstateScore, OPKO 4Kscore Test, and PCA3 as helpful options. Following biopsy, several tissue tests can be used to determine disease aggressiveness, including ConfirmMDx, Decipher Prostate Biopsy, Prolaris, and the Oncotype DX genomic prostate score test.

"[These tests] are used after the biopsy. This is taking the biopsy of someone with known prostate cancer and deciding whether this a cancer, based on the characteristics beyond Gleason score, PSA, and digital rectal exam, that can be watched or that requires further testing," Gomella said. There is no established testing strategy for patients with prostate cancer and each assay has its advantages and limitations (TABLE).

Turning to treatment implications, Gomella explained that in the setting of heavily pretreated metastatic castration-resistant prostate cancer, in the presence of a germline or somatic BRCA1/2 mutation or homologous recombination repair gene mutation, patients may be eligible to receive rucaparib (Rubraca) or olaparib (Lynparza), respectively. In the presence of high microsatellite instability/mismatch repair deficiency or tumor mutational burden greater than 10 mutations/Mb, pembrolizumab (Keytruda) may be considered.

"Many of the new treatments under study today are associated with precision medicine with the identification of a precise marker that can be used to guide treatment," Gomella said.

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"Many of the new treatments under study today are associated with precision medicine with the identification of a precise marker that can be used to guide treatment," Gomella said.

### TABLE. Advantages and Limitations of Tumor Profiling Tests

<table>
<thead>
<tr>
<th>Somatic tumor profiling</th>
<th>Germline testing</th>
<th>ctDNA analysis</th>
</tr>
</thead>
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<td>• Can be leveraged to identify patients eligible for treatment with olaparib or other targeted therapies</td>
<td>• Genes associated with hereditary prostate cancer included in large panel</td>
<td>• Identify somatic variations for targeted therapies including olaparib</td>
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<tr>
<td>• Information about translocations and amplifications</td>
<td>• Detection of germline variants</td>
<td>• Information on subclonal populations</td>
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<td>• Panels of &gt;300 genes</td>
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<td>• Moderate panel size of &lt;100 genes</td>
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<tr>
<td>• Information on TMB</td>
<td>• Tumor heterogeneity and temporal evolution may miss late somatic mutations in DNA-repair genes</td>
<td>• Limited information on amplification or translocations</td>
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**PRO**

- • Missing somatic or translocation/amplification that may guide treatment selection
- • Gene associated with hereditary prostate cancer included in large panel
- • Detection of germline variants

**CON**

- • Missing somatic or translocation/amplification that may guide treatment selection
- • Genes associated with hereditary prostate cancer included in large panel
- • Detection of germline variants

**ctDNA**, circulating tumor DNA; TMB, tumor mutational burden.

### FIGURE. Recommended Guidelines for Selection of Patients With Prostate Cancer to Undergo Genetic Testing and Counseling

- ≥2 cases of prostate cancer in close relatives ≤55 years regardless of risk category
- ≥3 first-degree relatives with prostate cancer regardless of risk
- Aggressive prostate cancer with a Gleason score ≥7
- ≥2 cases of breast, ovarian, and/or pancreatic cancer in a close relative
- Diagnosis of metastatic prostate cancer or metastatic castration-resistant prostate cancer
- Diagnosis of intraductal/cribriform prostate cancer
- Consider in conjunction with active surveillance
- Somatic tumor sequencing reveal mutations in hereditary cancer genes
- Ashkenazi Jewish ancestry
- Family history of cancer at an early age of diagnosis, including the following:
  - Breast cancer (<45 years)
  - Uterine or colon cancer (<50 years)
  - Ovarian cancer (<60 years)
- ≥2 cases of prostate cancer in close relatives ≤55 years regardless of risk category
- ≥3 first-degree relatives with prostate cancer regardless of risk
- Aggressive prostate cancer with a Gleason score ≥7
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TUNE IN!

In our exclusive interview, Aditya Bardia, MD, MPH, discusses how the latest data from DESTINY-Breast03 (NCT03529110), HER2CLIMB (NCT02614794), and NALA (NCT01808573) trials will affect clinical practice.
Investigators Look Beyond Immune Checkpoint Inhibitors to Chase Moving Targets in Prostate Cancer

by BRITTANY LOVELY

IMMUNE CHECKPOINT INHIBITORS represent only 1 area of effective therapy for patients with advanced prostate cancer, but they are not the be-all and end-all of immunotherapy options, according to Susan F. Slovin, MD, PhD. In a poll ahead of her presentation at the New York GU: 15th Annual Interdisciplinary Prostate Cancer Congress® and Other GU Malignancies, Slovin asked the audience their preferred antigen-targeted therapy for patients with advanced disease. In response, 50% of participants at the meeting said they would choose an antibody-drug conjugate with a chemotherapy payload.1

Slovin, who is associate vice chair of academic administration in the Department of Medicine at Memorial Sloan Kettering Cancer Center, in New York, New York, commented that these results might stem from the allure of targeting prostate-specific membrane antigen (PSMA) and the latest data on the Lutetium-177 (Lutathera), a radiolgand therapy that delivers β-particle radiation to PSMA-expressing cells and the surrounding microenvironment.2 “That is not pure immunotherapy, and a lot of [individuals] are under the misapprehension that it is,” Slovin said. “Lutetium-177 is a targeted therapy. [It] may have some immune mechanism and it gets internalized into the cell, but it is [not] what we call immunotherapy.”

In terms of what does constitute immunotherapy in prostate cancer, Slovin noted that identifying a target is only 1 step of the process. Overcoming resistance to engage it represents the greatest challenge in the field. “There are a lot of different antigens on the surface of tumor cells in prostate cancer, but are all of them targetable? Is their expression stable, or is it constantly ephemeral? If you are going to target a tumor antigen, [you must] find one where an antitumor effect [is possible]. It’s hard to know the relevance of a particular molecule just by virtue of it being there. We don’t really know if it’s targetable.”

TUMOR ANTIGEN IS NOT EQUAL TO THE TUMOR MICROENVIRONMENT

Prostate cancer is often referred to as a bland or cold disease, Slovin explained. However, a lack of expression on immune cells is only the tip of the iceberg from discovering and acting upon targets. Several immunosuppressive factors within the tumor microenvironment prevent the transformation to a hot or inflamed environment, including cancer-associated fibroblasts, T regulatory cells, and inhibitory molecules such as adenosine.

The presence of CD8-positive T cells in the tumor microenvironment has been described in 3 scenarios: desert, in which T cells are absent from the tumor and its periphery; excluded, in which the T cells have accumulated but do not efficiently infiltrate the tumor; and inflamed, in which the T cells infiltrate but their effects are inhibited.2 Approaches to overcome resistance to facilitate immune infiltration include oncolytic viruses, which promote T-cell priming; adoptive cellular therapies that promote T-cell expansion; and TFG8 inhibitors, which promote T-cell trafficking and infiltration.3,4 “Tumor cells are covered with a variety of different cells, [such as] macrophages, inhibitory cytokines, inhibitory T cells, adenosine—how do you get through? It’s not easy,” Slovin said. “For each aspect, if you are trying to develop strategies, each type of approach is going to be correlated with trying to get into the tumor cells through those inhibitory molecules or cells or cytokines. [For example], vaccines work by increasing antigen-presenting cells and trying to get the T cells to see [and learn] the molecule, and then go out and kill adoptive T-cell therapy.”

Slovin added that tactics such as checkpoint blockade have demonstrated some antitumor effects in patients with microsatellite instability-high disease, but in general, the response has been very suboptimal. Most recently, results of the phase 2 IMPACT trial (NCT03570619), which evaluated dual checkpoint inhibition with nivolumab (Opdivo) and ipilimumab (Yervoy) in patients with CDK12 inactivation or mutated metastatic castration-resistant prostate cancer (mCRPC) showed that only 14.2% (n = 4/28) of patients had a reduction of prostate-specific antigen (PSA) of at least 50%. Further, results showed that 6 patients (21.4%) had a 10-fold rapid increase in PSA over baseline.1

“[These data are] interesting because despite the information presented [in Cell on the prevalence of CDK12], which indicated that these tumors were highly responsive to nivolumab or [pembrolizumab (Keytruda)], investigators of the phase 2 trial didn’t see any signal,” Slovin said. “[It was] very surprising.”

LEVERAGING LESSONS LEARNED FROM PSMA

Overexpressed in resistant disease, PSMA represents a favorable target for both immune and radiographic therapies for prostate cancer. The focus of development in immunotherapies targeted PSMA are bispecific T-cell engagers (BiTEs) and chimeric antigen receptor (CAR) T-cell therapies. However, investigators are looking to build on the efficacy observed with such therapies leveraging PSMA to develop novel approaches.

“There are a lot of different antigens on the surface of tumor cells in prostate cancer, but are all of them targetable? Is their expression stable, or is it constantly ephemeral? If you are going to target a tumor antigen, [you must] find one where an antitumor effect [is possible]. It’s hard to know the relevance of a particular molecule just by virtue of it being there. We don’t really know if it’s targetable.”

— SUSAN F. SLOVIN, MD, PhD
**BITEs**

BITE therapies are designed with 2 flexibly linked, single-chain antibodies that simultaneously bind to targets on cancer cells and CD3 expressed on T cells, which results in T-cell infiltration, activation, cytokine production, and induced apoptosis.1,2 What’s interesting about BITEs is that it’s an off-the-shelf product. You don’t have to custom tailor it or initiate leukemia BITEs is that it’s an off-the-shelf product. You don’t have to custom tailor it or initiate leukemia.

Slovin is investigating new approaches to the leveraging CAR T-cell therapies targeting PSMA with the novel product P-PSMA-101 in a phase 1 trial (NCT04249947). The therapy is manufactured using a nonviral transposon system, facturing durability of these molecules so they can activate, proliferate, and have antitumor effects. The molecule is changed to add a fragment crystallizable region—which is literally the tail—and that gives stability and longevity to the molecule. Patients with metastatic de novo or treatment-emergent neuroendocrine prostate cancer who had disease progression following at least 1 line of prior therapy are eligible for enrollment to the study.3

**CAR T-Cell Therapies**

Slovin is investigating new approaches to the leveraging CAR T-cell therapies targeting PSMA with the novel product P-PSMA-101 in a phase 1 trial (NCT04249947). The therapy is manufactured using a nonviral transposon system, resulting in a high percentage of stem cell-like memory T cells, which engraft in bone marrow and are a key to CAR T-cell therapy success.4

**Neoadjuvant Chemotherapy Benefit Retains Stronghold for Patients With MIBC, UTUC**

**by JACKIE COLLINS**

**EFFECTIVE TREATMENT PATHS**

Leveraging neoadjuvant chemotherapy have been well established for patients with muscle-invasive bladder cancer (MIBC), with mounting retrospective and prospective data continuing to demonstrate overall survival benefit compared with adjuvant chemotherapy. Not only does treatment confer enhanced survival outcomes, but biologic information garnered from treatment also provides investigators with prognostic information to further refine treatment regimens, according to Jean Heather Hoffman-Censits, MD.

“Across the board, there is some consistency in terms of the pathological complete response [pCR]—somewhere between 20% and 40%—and the ability to safely get to surgery, which has always been a concern with cisplatin-based chemotherapy,” Hoffman-Censits said during a presentation at the New York GU*, 15th Annual Interdisciplinary Prostate Cancer Congress® and Other GU Malignancies.1 Hoffman-Censits is the codirector of the Upper Tract Urothelial Cancer Multidisciplinary Clinic at Johns Hopkins Medicine in Baltimore, Maryland. In her presentation, Hoffman-Censits reviewed the latest data supporting treatment pathways for patients with muscle-invasive or upper tract urothelial cancers.

**NEOADJUVANT THERAPY IS PREFERRED FOR MIBC**

Efforts to optimize the benefit of neoadjuvant chemotherapy among patients with muscle-invasive urothelial carcinoma have been undertaken in the phase 3 VESPER trial (NCT01812369). The trial was designed to compare outcomes between 6 cycles of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) and 4 cycles of gemcitabine and cisplatin (GC) as neoadjuvant chemotherapy. The trial also included a cohort of patients who received adjuvant chemotherapy.2 Hoffman-Censits first reviewed the data that supported the conclusion that both regimens of neoadjuvant chemotherapy were better tolerated than adjuvant chemotherapy, with 58% of patients (n = 127/218) completing 6 cycles of dd-MVAC and 66% of patients (n = 144/219) completing 4 cycles of GC compared with 37% (n = 11/30) and 46% (n = 12/26) in the adjuvant group, respectively. “This reinforces what we have seen in the clinic—adjuvant chemotherapy does not seem to be as well tolerated,” Hoffman-Censits said.

In the neoadjuvant group, pCR (ypT0pN0) was observed in 84 (42%) and 71 (36%) patients who received dd-MVAC and GC, respectively (P = .0221). A non-muscle-invasive status (< ypT2pN0) was achieved in 126 (63%) and 98 (49%) patients, respectively (P = .007). An organ-confined status (< ypT3pN0) was obtained in 154 (77%) and 124 (63%) patients, respectively (P = .001).

Most of the grade 3 or higher Common Terminology Criteria for Adverse Events (CTCAEs) concerned hematologic toxicities, which were reported in 129 (52%) patients in the dd-MVAC group and 134 (55%) patients in the GC group. Other reported grade 3 or higher CTCAEs were anemia (22% vs 7.8%; P < .0001), neutropenia (39% vs 46%; P = .14), febrile neutropenia (6.5% vs 2.4%; P = .02).

As of the December 31, 2021, cutoff date, 14 patients had received a single infusion of P-PSMA-101, ranging from 0.25 × 10^9 to 2.0 × 10^9 T cells. The median age was 71 years (range, 57-79). PSA response of at least 30% was observed in 6 patients (42.9%), and PSA response of at least 50% was observed in 5 patients (35.7%). In total, 10 patients (71%) had PSA decrease of any level. “CAR T-cell therapies that have tropism for bone-predominant tumors have therapeutic potential,” Slovin said.

In her conclusions, Slovin noted that immunotherapy is alive and well in prostate cancer, but that more insight to the mechanisms of cell-to-cell and cell-to-stromal interactions require more focus. Additionally, she emphasized the importance of biopsy, genomic profiling, and the use of companion imaging diagnostics for patients. “You need companion imaging. It is extremely important, because it is giving you a window into where the activity lies or no longer lies,” she said.

For a full list of references, see the article at OneLive.com
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P = .053), and thrombopenia (20% vs 17%; P = .50), respectively.

Hoffman-Censits noted that findings from a review of clinical trials evaluating immuno-therapy treatments including single agents, immuno-oncology (IO) combinations, and IO plus chemotherapy combinations in the neoadjuvant setting showed similar efficacy across populations, including among cisplatin-eligible and cisplatin-ineligible patients.

"What is striking is that no matter what the study or what the regimen, the pCR across the board is pretty similar," Hoffman-Censits said. "We are seeing a common theme in terms of neoadjuvant treatment and pCR outcomes. The addition of chemotherapy increases that pCR but not so significantly."

Notably, Hoffman-Censits referenced the phase 2 HCRN GU 16-257 trial (NCT03558087), in which patients with cT2-T4aN0M0 MIBC who were cisplatin eligible received 4 cycles of gemcitabine, cisplatin, and nivolumab (Opdivo), followed by clinical restaging, including urine cytology, MRI/CT of the bladder, cystoscopy, and bladder/prostatic urethral biopsies. Patients achieving a clinical complete response (cCR), which included a normal grading. Further, investigators presented with 63% of patients experiencing tumor downstaging. Patients achieving cCR, which included a normal grading, and cTO/Ta, were eligible to proceed without cystectomy and receive nivolumab twice weekly for 8 weeks, followed by surveillance; otherwise, patients underwent cystectomy.

At 1 year, 31 of 64 patients who underwent restaging achieved a cCR and an estimated 81.2% of patients were alive with bladder intact at 1 year (95% CI, 60.4%-95.8%). Among those who did not achieve cCR (n = 33), 11% were alive with bladder intact at 1 year (95% CI, 2.9%-91.7%).

Hoffman-Censits noted that more data are eagerly awaited with neoadjuvant immunotherapy and its role in bladder preservation, with preselected trials leveraging markers such as DNA mismatch repair, as well as unsel ected trials evaluating single-agent and combination regimens. "There are various randomized phase 3 trials that are completed, maturing, or ongoing that may impact the standard of care and this discussion maybe a year from now," she said.

NEOADJUVANT TREATMENT STRIKES BENEFIT IN UPPER-TRACT UROTHELIAL CANCER

Hoffman-Censits noted that up-staging remains a common problem in the diagnosis of bladder cancer. This is particularly evident among patients with upper tract urothelial cancer (UTUC). "[High-grade] tumors in the upper tract that are in [the] ureter or in the renal pelvis are excessively difficult to biopsy and stage," she said. "The expectation that you would get the same staging as you would in MIBC is not there. It is uncommon that a [bit] of muscle would come out of one of those biopsies."

In the preoperative setting, approximately 58% of patients may be eligible for cisplatin-based chemotherapy, Hoffman-Censits noted. However, after nephroureterectomy and lymph node resection, the eligible percentage drops to approximately 15%.

Data from preoperative trials demonstrated that the benefit of 4 cycles of neoadjuvant chemotherapy resulted in tumor downstaging and complete response rates for patients with high-grade clinically invasive UTUC.

In the phase 2 ECOG-ACRIN 8141 NAC trial (NCT02412670), 29 patients with baseline creatinine clearance greater than 50 mL per minute were assigned to 4 neoadjuvant chemotherapy cycles of accelerated methotrexate, vinblastine, doxorubicin, and cisplatin. Eight percent of patients completed all planned treatments, 10.3% achieved ypT0N0, and 1 achieved ypT0Nx, for a recorded pCR in 13.8% (90% CI, 4.9%-28.8%). Tumor downstaging to at least ypT1 was observed in 18 patients (62%).

Outcomes were similar for patients treated with neoadjuvant gemcitabine and cisplatin in a phase 2 trial (NCT01261728). At the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium, final results were presented and showed that among 57 treated patients, the overall pCR was 19%, with 63% of patients experiencing tumor downgrading. Further, investigators presented progression-free survival (PFS) and overall survival (OS) data for survivors that showed, when stratified by pathologic response, those with tumors stage lower than stage ypT2N0 who had a complete or partial response had significantly higher PFS and OS outcomes (P < .001). The 2-year PFS rate for responders (n = 36) was 91% vs 52% for nonresponders (n = 21), and the 2-year OS rate was 100% vs 80%. "The rate of pCR does correlate with PFS and OS, so this is important information, as we are, again, considering whether patients would be eligible for additional treatment in the adjuvant setting," Hoffman-Censits said.

ADJUVANT TREATMENT EXPLORATIONS REMAIN CRUCIAL

Investigators of the phase 3 POUT trial (NCT01993797) evaluated adjuvant chemotherapy, a favored approach in Europe, among patients with UTUC after nephroureterectomy. Patients with disease staged as either pT2-T4 pN0-N3 M0 or pTany N1-3 M0 were randomly assigned surveillance (n = 129) or four 21-day cycles of adjuvant chemotherapy, which was either cisplatin or carboplatin (n = 132).

Results showed that adjuvant chemotherapy significantly improved disease-free survival (DFS) (HR, 0.45; 95% CI, 0.30-0.68; P = .0001) at a median follow-up of 30.3 months (range, 18.0-47.5). Three-year event-free estimates were 71% (95% CI, 61%-78%) and 46% (95% CI, 36%-56%) for chemotherapy and surveillance, respectively. Noting these outcomes, Hoffman-Censits said chemotherapy tolerance has an advantage in the neoadjuvant setting, but that these data were not powered for comparison.

In ECOG-ACRIN 8141 NAC (n = 30), 90% of patients completed 4 cycles of cisplatin and 80% completed 4 cycles. In the phase 2 trial of gemcitabine/cisplatin (n = 53), 96% of patients completed 3 cycles of treatment and 83% completed 4 cycles. In the data from POUT, among the 76 patients assigned to gemcitabine/cisplatin, 71 started treatment, with 67% of patients completing 3 cycles and 59% completing 4 cycles.

Of note, 13% switched from cisplatin to carboplatin on study. "Just because the data do not necessarily support adjuvant therapy, there is still support to consider adjuvant therapy for these patients. That should not be forgotten," Hoffman-Censits said.

In MIBC, Hoffman-Censits noted that data from the phase 3 CheckMate 274 trial (NCT02632409) examined the role of checkpoint inhibitors in patients who received cisplatin in the neoadjuvant setting or were ineligible for cisplatin. Patients were randomly assigned 1:1 to nivolumab (n = 353) or placebo (n = 356) every 2 weeks for up to 1 year, following radical cystectomy. Of note, 20% of patients in the trial had UTUC.

The percentage of patients who had DFS at 6 months was 74.9% (95% CI, 69.9%-79.2%) with nivolumab and 60.3% (95% CI, 54.9%-65.3%) with placebo. At 12 months, these rates were 62.8% (95% CI, 57.3%-67.8%) and 46.6% (95% CI, 41.1%-51.9%), respectively (HR, 0.70; 98.22% CI, 0.55-0.90; P < .001).

Among patients with a PD-L1 expression level of 1% or more, the percentage of patients who had DFS at 6 months was 74.5% (95% CI, 66.2%-81.1%) and 55.7% (95% CI, 46.8%-63.6%), respectively. At 12 months, these rates were 67.2% (95% CI, 58.4%-65.3%) and 45.9% (95% CI, 37.1%-54.2%), respectively (HR, 0.55; 98.72% CI, 0.35-0.85; P < .001). "Based on the intention-to-treat analysis, adjuvant nivolumab for selected patients who meet [these] high-risk criteria is now guideline endorsed," Hoffman-Censits said.

For a full list of references, see the article at OncLive.com.
Analyze testing strategies that may inform clinical decision making in the management of hematologic malignancies

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Implement optimal strategies to treat hematologic malignancies

Assess disparities in care for patients with hematologic malignancies

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Trimodality Approach to MIBC Paves Path for Bladder Preservation

by ONCLIVE® STAFF

FOR PATIENTS WITH MUSCLE-INVASIVE bladder cancer (MIBC) who desire to pursue bladder-preserving approaches to care, chemoradiation therapy (CRT) is the recommended approach across guidelines.1,2 Standard CRT regimens have had marked success for patients with MIBC. However, up to 30% of patients who receive treatment with bladder-preserving intent will have recurrence.3

An unanswered question for patients with MIBC is the identification of an optimal CRT regimen. Following transurethral resection of a bladder tumor (TURBT), the recommended chemotherapy backbones for CRT from the National Comprehensive Cancer Network guidelines include 5-fluorouracil (5-FU) plus mitomycin; cisplatin, either alone or in combination with 5-FU, or paclitaxel; and low-dose gemcitabine.4 Additionally, the standard doses of radiation therapy are 1.8 to 2.0 Gy daily fractionation.

Approaches to build on investigator’s choice of CRT look to leverage immunotherapy, the first choice of which is the anti–PD-1 agent, pembrolizumab (Keytruda), which has demonstrated efficacy as a treatment prior to radical cystectomy in patients with MIBC. Specifically, in data from a phase 2 study (NCT02736266) evaluating single-agent neoadjuvant pembrolizumab, tumor downstaging to pT0 or pT1 was observed among 55% (95% CI, 46%-65%) of the 114 treated patients.3 Synergistic effects of anti-PD-1 blockade with chemotherapy and radiotherapy, respectively, have been reported.4 Investigators have undertaken efforts to demonstrate that this efficacy and tolerability extends to CRT.5,6

EARLY DATA SIGNAL STRONG START

ANZUP 1502 (NCT02662062) is a phase 2 trial of pembrolizumab (Keytruda) in combination with CRT in patients with MIBC who have undergone maximal resection with TURBT, are eligible for bladder preservation, or are unable to undergo cystectomy.

Among the first 10 patients who received treatment, the complete response rate was 90% at week 31.7 Investigators also noted a manageable safety profile with the combination, with urinary frequency, hematuria, anemia, urinary sepsis, and hypertension reported as the only grade 3 adverse effects (AEs). Additionally, no grade 3 or 4 immune-related toxicities were reported.

Further, data from a phase 2 trial (NCT02621151) of pembrolizumab, gemcitabine, and concurrent hypofractionated radiation therapy showed promising efficacy in both the safety and efficacy populations.8 Notably, among the 6 patients enrolled to the safety cohort, the complete response rate was 83%, with 1 patient not evaluable because of missed cytology or biopsy. Additionally, in the safety cohort, 1 patient experienced dose-limited toxicity that was immune related (grade 2 diarrhea) and was treated with corticosteroids. Among the 48 patients enrolled to the phase 2 efficacy cohort, 85% completed therapy.4

In results presented at the 2021 American Society of Clinical Oncology Annual Meeting, investigators noted that differences were observed in the data for the primary efficacy end point when patients were stratified by protocol-defined criteria and clinical practice criteria. When using the protocol criteria, the definition for post-radiation therapy response required all patients to get a complete the following: cystoscopy, a transurethral resection biopsy of the tumor site, and cytology. The CR rate for patients who met the criteria was 56%, with a partial response rate of 8.3%. One patient had disease progression and 10 were not evaluable based on the established criteria for the primary end point.4

Investigators notes, however, that these patients had visibly normal cystoscopy, and a normal cytology, which in practice, would be considered clinical CRs.

Specifically, 77% of patients had a recorded CR, with 8.3% maintaining a partial response. When combined with the safety population (n = 54), the CR rate was 80%. In terms of the dual primary end point of bladder-intact disease-free survival, the estimated 1-year rate was 88% (95% CI, 73%-95%) at a median follow-up of 14.6 months (range, 1.6-32.3). In a key secondary end point analysis, the estimated 1-year metastasis-free survival (MFS) rate was 85% (95% CI, 71%-93%) among all-treated patients in both cohorts.6

Building on these findings, investigators have initiated a phase 3 trial to further evaluate and

FIGURE. Trimodality Approach for Bladder Preservation in MIBC7

END POINTS

Primary
- BI-EFS
Key Secondary
- OS
Secondary
- MFS
- Time to occurrence of NMIBC
- Time to cystectomy
- PROs
- Safety
- Tolerability

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Bi-EFS, bladder-intact event-free survival; CRT, chemoradiation therapy; IV, intravenously; MIBC, muscle invasive bladder cancer; MFS, metastasis-free survival; NMIBC, non–muscle invasive bladder cancer; OS, overall survival; PROs, patient-reported outcomes; TURBT, transurethral resection of the bladder tumor.

Bi-EFS, bladder-intact event-free survival; CRT, chemoradiation therapy; IV, intravenously; MIBC, muscle invasive bladder cancer; MFS, metastasis-free survival; NMIBC, non–muscle invasive bladder cancer; OS, overall survival; PROs, patient-reported outcomes; TURBT, transurethral resection of the bladder tumor.
better define the role a trimodality approach may have in the treatment landscape for these patients.

**MOVING RESULTS INTO PHASE 3**

In the phase 3 KEYNOTE-922 trial (NCT04241185), investigators will randomly assign up to 636 patients with MIBC to CRT with or without pembrolizumab (FIGURE).7 The radiation therapy will be administered as either conventional schedule of 64 Gy administered to the individual’s bladder or bladder and pelvic nodes with 32 fractions administered over 6.5 weeks. Participants could also receive hypofractionated radiotherapy, which would consist of 55 Gy of radiation administered to the bladder with 24 fractions administered over 4 weeks.

Patients who are assigned to the investigative arm will receive pembrolizumab at 400 mg intravenously once every 6 weeks. Treatment will continue with pembrolizumab or placebo for up to 9 doses.7,8

Investigators will stratify patients by ECOG status, PD-L1 combined score (< 10 vs ≥ 10), anti–PD-L1, or agent directed at a stimulatory or coinhibitory T-cell receptor are not eligible.

In terms of eligibility for the trial, protocols states that patients must have MIBC that is not metastatic (N0M0) and has planned CRT that is inclusive of one of the protocol-specified radiosensitizing chemotherapy regimens.

Additionally, individuals must have an ECOD performance status of 0, 1, or 2, and adequate organ function. Of note, those who have received prior therapy with an anti-PD-1, anti-PD-L1, or agent directed at a stimulatory or coinhibitory T-cell receptor are not eligible for enrollment.7

**REFERENCES**


**MORE ON OneLive.com**

**UPDATES ON THE LATEST DATA IN MIBC**

**Neoadjuvant Atezolizumab/Chemo Shows Encouraging Efficacy in MIBC**

Data published in the Journal of Clinical Oncology showed that the addition of atezolizumab (Tecentriq) to neoadjuvant gemcitabine and cisplatin showed a high-rate of non–muscle-invasive downstaging following radical cystectomy, which correlated with improved relapse-free survival and overall survival in patients with muscle-invasive bladder cancer (MIBC), according to data from a phase 2 trial (NCT02989584).

**Neoadjuvant Enfortumab Vedotin Demonstrates Encouraging Activity in Cisplatin-Ineligible MIBC**

Enfortumab vedotin (Padcev) elicited promising antitumor activity when used as neoadjuvant treatment in patients with muscle invasive bladder cancer (MIBC) who were not eligible for cisplatin, according to preliminary findings from cohort H of the phase 1b/2 EV-103 trial (NCT03788845) presented during the 2022 Genitourinary Cancers Symposium.

**Palbos on the Utilization of Nivolumab Following Cystectomy in MIBC**

Phillip Palbos, MD, PhD, assistant professor at the University of Michigan Health in Ann Arbor, discusses the utilization of adjuvant nivolumab (Opdivo) following cystectomy in high-risk, muscle-invasive bladder cancer (MIBC) in the phase 3 CheckMate 274 trial (NCT02632409).
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\(^\circledR\)—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\(^\circledR\) (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\(^\circledR\) 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\(^\circledR\). 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\(^\circledR\) due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT\(^\circledR\) as recommended. Administer RYBREVANT\(^\circledR\) via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT\(^\circledR\) 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\(^\circledR\) based on severity.

**Interstitial Lung Disease/Pneumonitis**

RYBREVANT\(^\circledR\) can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT\(^\circledR\), with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT\(^\circledR\) due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT\(^\circledR\) in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

**Dermatologic Adverse Reactions**

RYBREVANT\(^\circledR\) can cause rash (including dermatitis acnetiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT\(^\circledR\), 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\(^\circledR\) was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT\(^\circledR\).

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT\(^\circledR\). Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
Results for tough-to-treat disease

3.7% of patients achieved a CR
36% of patients achieved a PR

**ORR**

40% (95% CI: 29%, 51% (n=81))

* Efficacy was evaluated by ORR* and DOR*11

**MEDIAN DOR WAS 11.1 MONTHS**

(95% CI: 6.9, NE)*11

*CHRYSLIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBREVANT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBREVANT® was administered intravenously at 1050 mg for patients ≤80 kg or 1400 mg for patients >80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.11

*According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).11

*Based on Kaplan-Meier estimates.11

The safety of RYBREVANT® was evaluated in the CHRYSLIS* study (n=129):11

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryofetal toxicity.11
- 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%).11
- 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 decreased sodium (4%).11
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion.16

*Based on the safety population, N=302.

The innovation you’ve been waiting for.

RYBREVANThcp.com

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 RYBREVANT® based on severity.

**Ocular Toxicity**

RYBREVANT® 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 RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

**Embryofetal Toxicity**

Based on its mechanism of action and findings from animal models, RYBREVANT® 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 RYBREVANT®.

**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 decreased sodium (4%).11

Please see Brief Summary of full Prescribing Information for RYBREVANT® on subsequent pages.

RYBRENT (amivantamab-vnjw) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
RYBRENT 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 (2.1) in Full Prescribing Information], 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 [see Clinical Studies (14) in Full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
RYBRENT 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 [see Adverse Reactions], IRR occurred in 68% of patients treated with RYBRENT. 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 modulations due to IRR was 69% and 13% of patients permanently discontinued RYBRENT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBRENT as recommended [see Dosage and Administration (2.3) in Full Prescribing Information]; Administer RYBRENT via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.6) in Full Prescribing Information].

Monitor patients for any signs and symptoms of infusion reactions during RYBRENT 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 RYBRENT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Intestinal Lung Disease/Pneumonitis
RYBRENT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population [see Adverse Reactions], ILD/pneumonitis occurred in 3.3% of patients treated with RYBRENT, with 0.1% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBRENT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBRENT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (2.4) in Full Prescribing Information].

Dermatologic Adverse Reactions
RYBRENT can cause rash (including dermatitis aciform, pruritus and dry skin. Based on the safety population [see Adverse Reactions], rash occurred in 74% of patients treated with RYBRENT, 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 RYBRENT was permanently discontinued due to rash in 0.7% of patients [see Adverse Reactions].

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBRENT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBRENT. Advise patients to wear protective clothing and use broad-spectrum UV-A/UV-B sunscreen. Alcohol-free emollient cream is recommended for dry skin.

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 RYBRENT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Ocular Toxicity
RYBRENT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population [see Adverse Reactions], keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBRENT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBRENT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal models, RYBRENT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. 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 RYBRENT. [see Use in Specific Populations].

ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions [see Warnings and Precautions]
- Intestinal 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 RYBRENT as a single agent in the CHRYSLIS study in 399 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <60 kg) or 1400 mg (for patients ≥60 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBRENT, 31% 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 RYBRENT 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 RYBRENT, 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, 33% were White, and 23% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBRENT. 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%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBRENT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBRENT in ≥1% of patients were pneumonia, IRN, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBRENT due to an adverse reaction occurred in 76% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥3% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBRENT 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.
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 RYBREVENT in CHRYSALIS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVENT (N=136)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>84</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>27</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>47</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>37</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>26</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

- Rash: acne, dermatitis, dermatitis acnorm, eczema, eczema astetetic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis
- Fatigue: asthenia, fatigue
- Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
- Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
- 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
- Dyspnea: dyspnea, dyspnea exertional
- Cough: cough, productive cough, upper airway cough syndrome
- Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
- Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
- Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
- Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
- Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVENT 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 RYBREVENT in CHRYSALIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYBREVENT (N=136)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>79</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
<td>8</td>
<td></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 avnigmatamb products may be misleading.

In CHRYSALIS, 3 of the 286 (1%) patients who were treated with RYBREVENT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-avnigmatamb 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 RYBREVENT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVENT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVENT in pregnant women or animal data to assess the risk of RYBREVENT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and postnatal death in animals (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

No animal studies have been conducted to evaluate the effects of avnigmatamb in reproduction and fetal development; however, based on its mechanism of action, RYBREVENT 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 embryofetal 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-vmijw 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-vmijw 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 9% 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/UVC 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].

**Product of Ireland**

Manufactured by: Janssen Biotech, Inc.

Horsham, PA 19044

U.S. License Number 1884

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cp-213278v1
PATIENTS WITH HER2-POSITIVE metastatic breast cancer can have their treatments tailored based on the presence of active central nervous system (CNS) disease, thanks to substantial advances made in the past few years in small molecule inhibitors and macromolecule biologics, according to a presentation by Mark Pegram, MD, at the 39th Annual Miami Breast Cancer Conference.1,2

“Macromolecule biologics, such as monoclonal antibodies or antibody-drug conjugates (ADCs), can penetrate the blood-brain barrier, resulting in objective responses,” said Pegram, the Suzy Yuan-Huey Hung Endowed Professor of Medical Oncology and associate dean for clinical research quality at Stanford University School of Medicine in California. “Tucatinib [Tukysa]-based therapy improves overall survival (OS) for patients with HER2-positive breast cancer with brain metastases while maintaining overall health-related quality of life, with some potential benefit also seen in leptomeningeal involvement.”

There are several risk factors associated with brain metastasis, Pegram noted, including triple-negative histology, high histological grade, increased Ki-67, nodal involvement, number of metastatic sites, short time to distant relapse, a tumor size smaller than 2 cm, and young age.

Another risk factor, however, is HER2 gene amplification or overexpression. There is an approximate 4-time greater risk of CNS disease in HER2-positive disease, Pegram said, with brain metastasis appearing in approximately 50% of patients with HER2-positive metastatic disease. Within the HER2 subtype, the SystHERs Registry patients with HER2-positive metastatic disease, Pegram said, “Local therapy, [although] effective, does not prevent recurrence and can cause significant toxicities.”

**SYSTEMIC THERAPIES FOR BRAIN METASTASES**

The blood-brain barrier has long been a key obstacle to developing effective systemic therapies to treat patients with CNS disease. However, newer agents have shown signs of overcoming this challenge. Studies with trastuzumab have shown the ability of monoclonal antibodies to cross the blood-brain barrier. In these studies, a high-dose version of trastuzumab (Herceptin) was tested in combination with pertuzumab (Perjeta) for patients with HER2-positive metastatic breast cancer with progressive brain metastases, with promising results demonstrated in the phase 2 PATRICIA study (NCT02536339).3 Here, the CNS objective response rate (ORR) was 11% (95% CI, 3%-23%) and the median duration of response was 4.6 months in the 39 treated patients; the 4- and 6-month clinical benefit rates were 68% and 51%, respectively (TABLE 4,6-7).

The HER2-targeted ADC ado-trastuzumab emtansine (T-DM1; Kadcyla) has also shown efficacy in patients with brain metastases and HER2-positive metastatic breast cancer.4 ORRs in this retrospective study were similar between patients with brain metastases (n = 77; 35.1%) and for those without (n = 191; 38.3%), demonstrating the efficacy of ADCs in this space. Additionally, the disease control rates were 53.3% and 66.6%, respectively. The median OS was 14 months (95% CI, 12.2-15.8) in patients with brain metastases compared with 32 months (95% CI, 24.4-39.6) in those without (P < .0001).

The ability of ADCs to cross the blood-brain barrier to elicit intracranial responses was further demonstrated with fam-trastuzumab deruxtecan-nxki (Enahertu) in the phase 3 DESTINY-Breast03 study (NCT03529110), with intriguing efficacy noted in patients with brain metastases that was superior for trastuzumab deruxtecan over T-DM1.5 In data from this pivotal study, the intracranial response rate was 63.9% with trastuzumab deruxtecan (n = 261) compared with 33.3% for T-DM1 (n = 263) (TABLE 4,6-7). Moreover, trastuzumab deruxtecan remained superior to T-DM1 across several efficacy end points in addition to response for patients with brain metastases.

In addition to biologics, the small molecule inhibitor tucatinib, in combination with trastuzumab and capecitabine, has also demonstrated efficacy for patients with brain metastases in the HER2CLIMB study (NCT02614794).6 In this study, the confirmed intracranial ORR with tucatinib in combination with capecitabine and trastuzumab was 47.3% (n = 198) compared with 20.0% with placebo, trastuzumab, and capecitabine (n = 93) (TABLE 4,6-7). In updated results, this also translated to a marked improvement in progression-free survival and OS.7

**TABLE. CNS Responses With HER2-Targeted Agents in Breast Cancer and Brain Metastases**

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* Data is ORR-IC.

CNS, central nervous system; ORR, objective response rate; ORR-IC, intracranial objective response rate.

**5 cm.** In these findings, grade 3 or higher cognitive disturbances were seen in 3% of patients with SRS compared with 5% for WBRT, hearing impairment in 3% vs 9%, and grade 1/2 events in 16% vs 23%, respectively.

“Brain metastases often occur quickly during the course of HER2-positive metastatic breast cancer and negatively affect quality of life and OS,” Pegram said. “Local therapy, although effective, does not prevent recurrence and can cause significant toxicities.”

Brain Metastases Are Now More Treatable in HER2+ Metastatic Breast Cancer

by SILAS INMAN

The ability of ADCs to cross the blood-brain barrier to elicit intracranial responses was further demonstrated with fam-trastuzumab deruxtecan-nxki (Enahertu) in the phase 3 DESTINY-Breast03 study (NCT03529110), with intriguing efficacy noted in patients with brain metastases that was superior for trastuzumab deruxtecan over T-DM1. In data from this pivotal study, the intracranial response rate was 63.9% with trastuzumab deruxtecan (n = 261) compared with 33.3% for T-DM1 (n = 263) (TABLE 4,6-7). Moreover, trastuzumab deruxtecan remained superior to T-DM1 across several efficacy end points in addition to response for patients with brain metastases.

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This tucatinib regimen was also explored as a potential treatment for patients with HER2-positive breast cancer and leptomeningeal metastasis in the phase 2 TBCRC049 study (NCT03501979). In data from this study, 35% of the 17 enrolled patients remained alive at a median follow-up of 18 months. The median OS was 10 months (95% CI, 4.1-not reached) and the median time to CNS progression was 6.9 months (95% CI, 2.3-13.8).

“Following taxane, trastuzumab, and pertuzumab therapy, trastuzumab deruxtecan is now the preferred regimen for [individuals] without CNS disease,” Pegram said. “For those with active CNS disease, clearly [the combination of] tucatinib, trastuzumab, and capcitabine is a strong consideration, because there’s level 1 evidence of OS benefit with statistical confidence. For those with stable CNS disease, it is probably more of a toss-up.”

With these agents now available with proven efficacy in brain metastases, Pegram noted that screening guidelines should be updated to look for CNS involvement more frequently.

“Screening guidelines recommend screening for CNS metastases only in symptomatic patients, but this may not adequately capture all patients with brain metastases,” he concluded.

**REFERENCES**


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**Addressing Cardiotoxicity in Breast Cancer Requires Multifaceted Approach**

**by KYLE DOHERTY**

**PATIENTS WITH BREAST CANCER** who experience treatment-emergent cardiotoxicity should be evaluated using a team-oriented approach based on guideline-directed therapies, Jean-Bernard Durand, MD, FACP, FCCP, FACC, FHFS, said in a presentation during the 39th Annual Miami Breast Cancer Conference®.

“The predominant cardiotoxic medications in breast cancer are anthracycline-based therapies, tyrosine kinase inhibitors, trastuzumab [Herceptin], and pembrolizumab [Keytruda],” said Durand, who is a professor in the Department of Cardiology in the Division of Internal Medicine at The University of Texas MD Anderson Cancer Center (MD Anderson) in Houston. “The goals of treatment, from a cardiology perspective, are very simple: keep our patients alive, keep them feeling well, and keep them out of the hospital.”

An absolute 10-point decrease in left ventricle ejection fraction (LVEF) is a common measurement of cardiotoxicity. Durand outlined the current guideline-directed treatment paradigm for patients who are admitted with heart failure. The agents include treatment with targeting the renin-angiotensin-aldosterone system upon admission, followed by β-blockers, mineralocorticoids, and sodium-glucose cotransporter 2 inhibitors (SGLT-2s).

Durand contended that antidiabetic agents, such as SGLT-2s, can be very useful in treating cardiomyopathy, and data show they are equipped to play a much greater role for the treatment of cardiotoxicity. This is partially because there are similar pathophysiological features between diabetes and heart failure, the mechanistic effects of SGLT-2s—such as dapagliflozin (Farxiga) occurring in patients with and without diabetes—and the cardiovascular benefits of these agents being independent of glucose levels, Durand explained.

“I can promise you as oncologists, [over the next 2 years, you are going to be overwhelmed by the data on antidiabetic drugs and the beneficial effects they have] for cardiotoxicity and heart failure,” Durand said. “This is both [in terms of] preserving [ejection fraction] and a drop in [ejection fraction].”

For patients with breast cancer, treatment guidelines for the most used agents are in place for clinicians to monitor and address these adverse effects (AEs). For example, prior to the administration of trastuzumab, patients should undergo an evaluation for cardiac risk. If a patient is at risk of cardiotoxicity, the treating clinician should refer the patient to a cardio-oncologist. Following the initiation of treatment, the patient should be monitored for LVEF decreases every 3 months. Should a patient experience a decrease in LVEF of 10 or more points, they should be referred to a cardio-oncologist to begin either cardioprotective regimens, which may or may not require treatment with trastuzumab to stop.

**IMMUNOTHERAPY-RELATED CARDIAC EFFECTS**

Durand noted that immune-checkpoint inhibitors rarely have cardiac-related AEs, but those that do occur can be life-threatening. For example, myocarditis is reported in less than 1% of patients treated with immune-checkpoint...
inhibitors. However, the AE is associated with a mortality rate of up to 50%.\(^3,4\) Unfortunately, serious AEs such as myocarditis are unpredictable, Durand said, adding that early detection depends on recognizing nonspecific symptoms and close monitoring.

Durand noted that in MD Anderson’s cardiology department, patients with suspected myocarditis undergo a diagnostic workup consisting of laboratories, imaging, and procedures.\(^7\) After a biopsy, a pathologist should evaluate a variety of laboratory values, including troponin T, N-terminal pro-B-type natriuretic peptide, and creatine kinase, among others. The imaging workup consists of a 12-lead electrocardiogram, a single-view chest x-ray, a 2D/3D complete echocardiogram, and a cardiac MRI delayed 48 hours after symptom presentation. The procedural workup consists of a right and left heart catheterization with an endomyocardial biopsy.

When patients present with noncardiovascular immune-related AEs, clinicians should first check for troponin T, Durand said. If the patient does not have any clinical symptoms and the levels are less than 100, no further workup for myocarditis is needed. If troponin T levels are 100 or greater, clinicians should proceed to using the diagnostic and treatment algorithm for suspected myocarditis. “If you are in the community, remember to develop a team [for patient care],” Durand said.

**REFERENCES**


“The goals of treatment, from a cardiology perspective, are very simple: keep our patients alive, keep them feeling well, and keep them out of the hospital.”

— JEAN-BERNARD DURAND, MD, FACP, FCCP, FACC, FHFS
FOR YOUR ADULT PATIENTS WITH PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER

IF SHE RESPONDS TO CHEMOTHERAPY

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

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\(^1,2\)

**OVERALL POPULATION**
(N=733)

38% Reduction in the risk of progression or death

**HRd POPULATION**
(n=373)

57% Reduction in the risk of progression or death

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

**Important Safety Information (continued)**

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

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

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

Please see Brief Summary on the following pages.


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

Visit ZEJULAHCP.COM to explore the PRIMA data

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Produced in USA.
**Brief Summary of Prescribing Information**

**Zejula (niraparib)** capsules, for oral use

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

1 **INDICATIONS AND USAGE**

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

**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.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

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

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

**Zejula** is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status as determined by either:

- A deleterious or suspected deleterious BRCA mutation, or
- Genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy

(see Clinical Studies (14.3) of full prescribing information).

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

4 **CONTRAINDICATIONS**

None.

5 **WARNINGS AND PRECAUTIONS**

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received monotherapy with Zejula in clinical trials. In 1,785 patients treated with Zejula in clinical trials, MDS/AML occurred in 15 patients (0.8%).

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

5.2 Bone Marrow Suppression

Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or panhypoponopenia have been reported in patients treated with Zejula (see Adverse Reactions (6)).

In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 30%, 12%, and 20%, respectively, of patients receiving Zejula. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of Zejula based on baseline weight or platelet count, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 23%, and 15%, respectively, of patients receiving Zejula. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

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

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

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

5.3 Hypertension and Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with Zejula.

In PRIMA, Grade 3 to 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 331 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 adjust the dose of Zejula, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).

5.4 Posterior Reversible Encephalopathy Syndrome

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)). 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 reinitiating 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 actively dividing cells in animals and patients. Zejula should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

5.6 Allergic Reactions to FDA Yellow No. 5 (Tartrazine)

**Zejula** capsules contain FDA Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FDA 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 1,314 patients who received Zejula in the pooled Phase 3 trials, NOVA, NOVA-2, and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), diziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypoglycemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

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

All patients receiving Zejula in PRIMA. Serious adverse reactions occurred in 32% of patients receiving Zejula. Serious adverse reactions in ≥2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intussusception and pleural effusion (1 patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received Zejula. Adverse reactions resulting in permanent discontinuation in <3% of patients who received Zejula included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2%) each. Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (55%), and neutropenia (20%).

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

(continued on next page)
 Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA: Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanently discontinued due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions leading to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54 5 21 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>50 28 23 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36 8 15 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28 11 5 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53 21 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>31 15 1 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 9 0 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>87 66 29 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74 13 37 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66 57 3 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66 25 23 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51 29 7 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46 21 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40 23 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36 34 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35 17 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29 17 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81 70 21 0</td>
<td></td>
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<tr>
<td>Decreased leukocytes</td>
<td>70 36 6 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>63 15 18 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63 56 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>60 27 15 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52 30 5 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43 17 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44 30 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>42 22 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31 19 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28 15 2 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=244)</th>
<th>Placebo (n=367)</th>
<th>ZEJULA (n=244)</th>
<th>Placebo (n=367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in hematocrit</td>
<td>52 30 5 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43 17 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44 30 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>42 22 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31 19 1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28 15 2 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 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 indicated 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 (Grade 1 to 4) occurred in 21% of patients who received ZEJULA. Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

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

(continued on next page)
### 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 includes events with preferred terms of neutropenia.

**Gastrointestinal disorders:** Thrombocytopenia includes events with preferred terms of thrombocytopenia.

**Infections and infestations:** Urinary tract infection.

**Investigations:**
- Blood alkaline phosphatase.
- AST/ALT elevation.
- Increased AST/ALT.
- Increased alkaline phosphatase.
- Decreased albumin.
- Decreased neutrophils.
- Increased creatinine.
- Increased glucose.
- Decreased leukocytes.
- Decreased lymphocytes.
- Decreased platelets.

**Musculoskeletal and connective tissue disorders:** Decreased appetite.

**Nervous system disorders:**
- Hypersensitivity (including anaphylaxis).
- Insomnia.
- Nervous system disorders.

**Renal and urinary disorders:**
- Decreased albumin.
- Decreased creatinine.
- Decreased hemoglobin.
- Increased blood urea nitrogen.

**Respiratory, thoracic and mediastinal disorders:**
- Acute kidney injury.
- Abnormal Laboratory Finding.
- Decreased albumin.
- Increased creatinine.
- Decreased neutrophils.
- Increased glucose.

**Skin and Subcutaneous Tissue Disorders:**
- Hypersensitivity.
- Urinary tract infection.
- Infertility.

**Non-infectious and vasculitis syndromes:**
- Hypertensive crisis.
- Myelodysplastic Syndrome/Acute Myeloid Leukemia.

**Vascular Disorders:**
- Myocardial infarction.
- Pneumonitis.

**Other disorders:**
- Myelodysplastic Syndrome/Acute Myeloid Leukemia.

### 6.3 Administration and Clinical Use

Advise patients to contact their healthcare provider for new onset of bleeding, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts or a need for blood transfusions. This may be a sign of hematologic toxicity or MDS or AML, which has been reported in patients treated with ZEJULA.

## 7. حوالي

### Table 7. Adverse Reactions Reported in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51 27</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52 28</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 13</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67 10</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>44 8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>36 5</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34 7</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 0.2</td>
<td></td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

| Fatigue | 56 7 | |

### Table 8. Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83 26</td>
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<tr>
<td>Increased glucose</td>
<td>66 5</td>
<td></td>
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<tr>
<td>Decreased platelets</td>
<td>60 28</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57 18</td>
<td></td>
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<tr>
<td>Decreased leukocytes</td>
<td>53 9</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46 1</td>
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</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40 4</td>
<td></td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40 8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36 0.4</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34 6</td>
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<tr>
<td>Decreased neutrophils</td>
<td>34 15</td>
<td></td>
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<tr>
<td>Increased aspartate aminotransferase</td>
<td>29 2</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27 2</td>
<td></td>
</tr>
</tbody>
</table>
Pacritinib May Fill Unmet Symptom Burden Need for Patients With Myelofibrosis With Moderate/Severe Thrombocytopenia

by KYLE DOHERTY

PHYSICAL FUNCTION-RELATED SYMPTOMS WERE prominent in the symptom burden of adult patients with myelofibrosis and moderate or severe thrombocytopenia, according to a retrospective analysis of the phase 3 PERSIST-2 study (NCT02055781) presented at the National Comprehensive Cancer Network (NCCN) 2022 Annual Conference.

“Tiredness and inactivity represent the most prevalent burden for patients with myelofibrosis with moderate to severe thrombocytopenia,” Ruben A. Mesa, MD, the director of The University of Texas Health San Antonio MD Anderson Cancer Center, said.

Data from the analysis showed that tiredness was the most severe symptom in the overall population (N = 259) with a median symptom severity score of 6. Patients with moderate or severe baseline thrombocytopenia were included and stratified by baseline platelet count; 50-100 × 10^9/L (n = 118) vs less than 50 × 10^9/L (n = 141).

Patients with severe thrombocytopenia had a higher combined median score of tiredness plus inactivity compared with patients with moderate thrombocytopenia, 12 vs 10, respectively (P = .014).1

Investigators of the PERSIST-2 study (NCT02055781) evaluated the safety and efficacy of the oral JAK2 inhibitor pacritinib (Vonjo) in adult patients with primary or secondary myelofibrosis. To be eligible for the trial, patients needed to have a platelet count of 100 × 10^9/L or less. Prior treatment with a JAK2 inhibitor was permitted.

The trial randomized a total of 311 patients 1:1:1 to receive pacritinib 400 mg once daily, pacritinib 200 mg twice daily, or best available therapy. The coprimary end points of the trial were spleen volume response of at least a 35% at week 24 and at least a 50% total symptom score (TSS) reduction at week 24.

On February 28, 2022, the FDA granted pacritinib an accelerated approval for the treatment of adults with intermediate- or high-risk primary or myelofibrosis with a platelet count below 50 × 10^9/L. The approval was based on results from PERSIST-2.2

In the analysis presented at the NCCN 2022 Annual Conference, symptom scores were evaluated using TSS 2.0 and were averaged for the week prior to randomization. Symptom prevalence was defined by a symptom score of at least 1 on a scale of 1 to 10.

Patients in the moderate group had a median age of 69 years (range, 64-74) compared with 67 years (range, 62-74) in the severe group. The median platelet count in moderate group was 28 × 10^9/L (range, 18 × 10^9/L to 40 × 10^9/L) vs 70 × 10^9/L (range, 58 × 10^9/L to 82 × 10^9/L) among patients with a higher platelet count. Median hemoglobin was comparable in both arms, 9.2 g/dL (range 8.2 g/dL to 10.6 g/dL) and 9.4 g/dL (range, 8.4 g/dL to 11.0 g/dL) in the lower and higher platelet count arms, respectively. Patients with peripheral blasts of at least 1% were more common in the moderate cohort (48.2%) compared with the severe group (40.7%).

Patients with moderate thrombocytopenia had a mean TSS score of 22 and the average TSS score in this group was 23.7 (range, 4.0-58.4). Similarly, patients with severe thrombocytopenia had a median TSS score of 23 and the average TSS score was 25.7 (range, 3.0-64.3).

Additional results from the analysis showed that inactivity had a symptom severity score of approximately 5.5 and approximately 4.5 among patients in the moderate and severe cohorts, respectively. In terms of spleen-related symptom severity, patients with moderate thrombocytopenia had median symptom severity scores of approximately 3 for early satiety, approximately 3 for abdominal discomfort, and 2.5 for left rib pain. For patients with severe thrombocytopenia, these scores were approximately 5, approximately 4, and approximately 2, respectively.

Patients with moderate disease also had higher median symptom severity scores compared with those with severe disease for the cytokine-related symptoms of night sweats (approximately 3 vs approximately 2.5, respectively) and bone pain (approximately 2 vs approximately 1.5, respectively).

All symptoms examined in the analysis had a prevalence of at least 50% at both platelet levels. Common symptoms in the moderate group included tiredness (approximately 95%), inactivity (approximately 90%), early satiety (approximately 90%), abdominal discomfort (approximately 80%), and night sweats (approximately 70%). Among patients with severe thrombocytopenia common symptoms were made up of tiredness (approximately 95%), inactivity (approximately 85%), early satiety (approximately 85%), abdominal discomfort (approximately 75%), and night sweats (approximately 70%).

“As pivotal phase 2 studies for the JAK1/2 inhibitors ruxolitinib [Jakafi] and fedratinib [Inrebic] excluded patients based on lower platelet counts less than 50,000/µL or 100,000/µL, respectively, an unmet need remains for therapies that can improve symptomatic disease with myelofibrosis and limits the effect to their platelet count; pacritinib may fill this role,” Mesa said.

“These data are even more relevant in light of the recent approval of pacritinib for patients with a platelet count of less than 50,000/µL.”

Specifically, pacritinib showed a marked spleen volume reduction of at least 35% compared with BAT. Among Investigators individuals with a platelet count of less than 50 × 10^9/L, those who received pacritinib at the recommended 200-mg twice-daily dose (n = 31), 29.0% (95% CI, 14.2%-48.0%) had a reduction in symptom burden vs 3.1% (95% CI, 0.1%-16.2%) of those who received BAT (n = 32).3

In terms of TSS, 26% of patients who received pacritinib had a reduction of at least 50% using the Modified Myelofibrosis Symptom Assessment Form compared with 9% of those who received BAT.3

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

Ruben A. Mesa, MD, joins OncLive On Air® to discuss the data that led to the FDA approval of pacritinib (Vonjo), toxicities clinicians should be aware of when prescribing the JAK inhibitor, and the next steps for pacritinib in myelofibrosis.

TO LISTEN, SCAN THE QR CODE OR VISIT: bit.ly/375nSIY

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Data-Driven Health Economics Research Can Improve Clinical, Economic Outcomes

by KYLE DOHERTY

WITH IMPROVEMENTS IN electronic medical records (EMRs), telemedicine, and other digital health solutions, clinicians have access to more data than ever to help inform decisions. New metrics such as patient volume, location, and details of treatment trajectory can help practices improve their care from a clinical standpoint, according to Lalan Wilfong, MD. But how best to leverage the economic influence of these data on clinical practice and patient outcomes remains an area of exploration.

“Practices [must] figure out how to better understand the economics of what they do, especially as the field moves to more total cost of care models and more value-based care models, where we are more accountable for the cost we give [to the patient] and how we spend the [associated] revenue,” Wilfong said in an interview with OncologyLive®.

Wilfong, a medical oncologist and hematologist with Texas Oncology and vice president for payer relations and practice transformation at McKesson Specialty Health, both in Dallas, Texas, said using data to retain patients from time of diagnosis through completion of therapy is a key factor in a practice’s financial stability. Data-driven health economics and outcomes research offers clinicians effective methods for improving quality of life and outcomes for patients and optimizing economic benefits for the practice.

“Quality metrics have influenced the way that we measure and perceive cancer care by focusing us more on what means most to patients, and how do we improve the outcomes that we provide vs just managing patients as we see is best,” Wilfong said. “Things [such as] metrics in the Oncology Care Model for reducing hospitalizations and reducing ED [emergency department] visits makes us think through the entire patient care continuum vs focusing on just what’s happening that day with a patient.”

STRATEGIES FOR IMPROVED METRICS

Health economics research has grown tremendously in community oncology over the past few years. Wilfong attributes that growth to the shift toward value-based care. “We had to show the benefit of the services we provided and really start thinking about the entire patient journey vs just individual data points, like we do in clinical research,” he said. “Health economic outcomes [helps us] understand risk profiling and what is the true value of the therapies we provide, not just monetarily, but also the patient’s quality of life and outcomes.”

The incorporation of machine learning and/or artificial intelligence in standard practice procedures may afford clinicians the chance to evaluate and optimize treatment economics. The SHEILD-RT study (NCT03775265) was among the first randomized prospective studies to implement machine learning as part of an interventional clinical application. The study used an EMR-based algorithm to identify patients at high risk of hospitalizations during radiotherapy or chemotherapy.1

The machine learning algorithm identified 311 patients with a greater than 10% risk of an acute care visit during radiotherapy at Duke University Hospital in Durham, North Carolina, between January 2019 and June 2019. Patients were randomized to receive a weekly evaluation during treatment (n = 157) or a twice-weekly evaluation during treatment (n = 154).1

Overall, a reduction in acute care visits for the total population was observed from 22% to 12%. Patients evaluated twice weekly experienced fewer hospitalizations and ED visits compared with patients in the once-weekly arm: 29 vs 41 and 18 vs 33, respectively. From an economic perspective, the study authors noted that costs were reduced across revenue centers and that machine learning has shown potential to enhance quality of care in addition to keeping costs down. Specifically, the overall mean cost of acute care during radiotherapy was reduced by $2063 (95% CI, 4-4119; P = .03) when patients were evaluated twice weekly. The largest mean difference was observed in inpatient costs ($1815; 95% CI, –129 to 3760; P = .05). Next steps include incorporating physician and intervention costs into the analysis.

Another potentially helpful data point clinicians may consider involves patient-reported outcomes (PROs), which can be added into the EMR and other digital health solutions to better inform treatment decisions. Data obtained at the patient level provides investigators with real-world insight that may help in understanding outcomes not observed in patients enrolled in clinical trials and assessing the unmet needs in preventing and treating adverse effects. Leveraging digital health solutions that can collect these data may improve the following:

- Communication between patients, providers, and their communities
- Patient and caregiver education
- Clinical assessment improvements for patient outcomes
- Self-monitoring education and uptake of self-management practices

SUPPORT OF REAL-WORLD ANALYSES OF PROS

In a qualitative review, Aapro et al sought to better understand the effect of PROs in oncology collected via electronic methods on routine supportive care in terms of clinical and health economic end points. In the analysis,
investigators reviewed 66 studies that included data from 38 unique digital health systems used to collect PROs via remote monitoring. Of note, 21 of the systems provided patients with self-management symptom support tactics.

Highlighting one of the pillars for improvement—communication—digital solutions that allow for self-reporting of symptoms can lead to a reduction in unexpected cost for the patient, greater use of hospital resources, and improved completion rates of treatment. For example, a single-center study cited in the analysis assessed outcomes of 766 patients who were randomized to receive email alert prompts to report symptoms experienced during their chemotherapy treatment at Memorial Sloan Kettering Cancer Center in New York, New York. Severe symptoms were reported by 63% of patients during the study and in response to email alerts of these symptoms, nurses initiated clinical action.

The authors also cited a decrease in ED and hospital admissions when digital health solutions were used to monitor patient outcomes. Specifically, among those who received the alert (n = 441), 34% were admitted to the ED compared with 41% of patients who received standard care (n = 325; P = .02).

Despite the observed benefits with PROs, the uptake of such solutions in practice present clinicians, patients, and supportive staff with additional hurdles. For example, integration of solutions in established systems takes time and adds an initial cost up front, not to mention that training and potential clinical trials evaluating efficacy may present delays in execution (TABLE). As far as improvement, I think it’s understanding all the disparate systems that we have to track, various economic metrics, and how we correlate those together into a unified platform,” Wilfong said.

Investigators of the analysis also supported that the effects of digital solutions on overall health care costs warrant further assessment. Wilfong noted that efforts are under way to assess the state of digital health systems at the practice level, but more efforts are needed to ensure that clinicians are making the most of data collected to influence financial change.

“For example, our practice management systems track new patients and revenue collection, our EMRs track the clinical activity around that, our pharmacy systems—which tend to be separate—track utilization, [and so on],” he said. “The biggest thing is figuring out what systems contain what data and [learning] how to piece that together and form a coherent model that drives financial outcomes.”

The data to determine the intensity of resources allocated to each patient depending on their diagnosis, treatment options, and comorbidities are not quite advanced enough yet, Wilfong said.

### TABLE. Benefits and Limitations of Digital Health Care Solutions for Stakeholders

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Benefits</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>• Provides a direct line to HCPs</td>
<td>• Barriers in technology availability/use</td>
</tr>
<tr>
<td></td>
<td>• Greater involvement in care decisions</td>
<td>• Potentially time consuming</td>
</tr>
<tr>
<td></td>
<td>• Relevant disease-related and treatment-related information always available</td>
<td>• Risk of depersonalization</td>
</tr>
<tr>
<td>Physicians</td>
<td>• Improved communication with patients</td>
<td>• Barriers in technology availability/use</td>
</tr>
<tr>
<td></td>
<td>• Shared decision-making by involving patients in the care process</td>
<td>• Time for patient communication needs to be allocated outside of normal hours</td>
</tr>
<tr>
<td></td>
<td>• Patient data collection in real time</td>
<td>• Changes in the organization of HCP teams</td>
</tr>
<tr>
<td></td>
<td>• Treatment toxicity management in real time</td>
<td>• Difficulties in changing usual practices of symptom management</td>
</tr>
<tr>
<td>Health care systems</td>
<td>• Reduction in ED visits, wait time in ED, and transportation costs</td>
<td>• Standardized practices and regulations are still developing</td>
</tr>
<tr>
<td></td>
<td>• Reduction in unplanned hospitalizations</td>
<td>• Need to expand and train HCPs to use digital solutions</td>
</tr>
<tr>
<td></td>
<td>• Prevention and treatment of AEs more consistent with guidelines</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; ED, emergency department; HCPs, health care professionals.

He noted that, although this problem is complex and challenging, efforts are under way to better understand how to leverage large data sets, such as those available from Medicare, to achieve appropriate cost allocation on a per-patient basis.

**COVID-19 CONTINUES TO CHANGE EVERYTHING**

Wilfong noted the profound effect the COVID-19 pandemic has had on how practices try to effectively provide care to patients, both from a quality of care and an economic standpoint. Clinicians and institutions are still working to fully quantify these changes, Wilfong said.

“[COVID-19 led to] a definite change in cancer screenings, which will translate to patients presenting with more advanced disease,” Wilfong said. “It is going to change the mix of staging [of our patients’ disease] that occurred because of the lack of ongoing provider visits and screenings.”

Although this presents the potential for cost increases because patients require more intensive treatment for their disease, the pandemic did provide some insight into improvements in care. “[What] the COVID-19 pandemic taught us was how to incorporate more digital health methods [and] resource allocation for those [is] very different from an economic standpoint,” Wilfong said.

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**Improving Financial Literacy Among Clinicians**

**THE PUBLIC DOES NOT** usually think of physicians as being financially stressed, but in many instances that is the case. In a recent study, investigators found that medical residents and fellows have low levels of financial literacy and high levels of debt. Nearly 33% of respondents indicated they struggle to find funds for monthly expenses, even though their median income is around the national average. Researchers concluded that training in budgeting, estate planning, investing, and retirement planning is essential for providing medical school students and physicians with the ability to effectively manage finances.

Results from a California Medical Association survey that appeared in *Physicians Weekly* in 2021 found that 64% of physicians expressed a need for financial assistance, 47% required temporary housing, and 95% of physician practices reported concern about their financial well-being.

Tips from the author to improve financial literacy include the following:

- Perform a cash flow exercise.
- Identify a percentage of expenses that can be eliminated or reduced.
- Set a time for depositing funds into a savings account.
- Find a trusted adviser.

To read the full story on Medical Economics®, scan the QR code or visit bit.ly/379mzhO
In a survey conducted by the American Society for Radiation Oncology, investigators sought to quantify the effect of the pandemic on radiation oncology practices. Wakefield et al reported that telemedicine use was new to 89.2% of physician leaders who responded in April 2020 (n = 222). Additionally, telemedicine use for routine surveillance visits increased from 74.3% in April 2020 to 85.5% for responding physician leaders in February 2021 (n = 117). By February 2021, over half (53.8%) of responders were using telemedicine for new patient consultations.1

In terms of economic considerations, telemedicine has been shown to reduce cancer care costs for patients by offsetting the cost of transportation to the clinic, parking fees, lost time at work, and more.2 For oncology practices, the costs of implementing the infrastructure to support a telemedicine system (EMRs, updating computer systems, and so on) may be cumbersome initially. However, Parikh et al used a time-driven, activity-based costing analysis to show that the transition to telemedicine saved a radiation oncology department an average of $586 per patient compared with the traditional workflow.4 The department saved an average of $347 for space and equipment and $239 in personnel costs.5 Several other cost analyses of the effect of telemedicine in oncology practice are maturing.

Community oncology practices should be aware that health care consumerism is also on the rise because of the pandemic, Wilfong said. Patients are beginning to question what they are getting out of their health care and how it can be improved, he added. Clinicians and institutions working at the community level must be prepared to adapt and continue to come up with innovative ways to ensure patients receive the best care from a clinical and consumer experience perspective in order to ensure continued economic viability, Wilfong said.

For example, a patient satisfaction survey from a large National Cancer Institute-designated cancer center by Natesan et al found that although overall patient satisfaction with telemedicine was high, different levels of satisfaction were observed across patient demographics. Patients born between 1981 and 1995 had higher satisfaction with telemedicine services (87%) compared with those born between 1965 and 1980 (77%) or 1946 and 1964 (74%).6

In another retrospective study of patient satisfaction with telemedicine during the pandemic, Swartz et al found that young adults with cancer (aged 18-39 years) had several suggestions for improving the experience. These included interpersonal communication, logistics, and addressing specific concerns with treatment, among others.7 Studies such as these underscore the fact that patients are demanding more from their care, especially after feeling the effects of the pandemic, and clinicians need to gather and apply as much as possible to better serve them.

“Understanding what data you have and understanding why [these] data are important can be 2 different questions,” Wilfong concluded. “Who are the stakeholders [who] need to see the data? How should those stakeholders see the data? You [must] understand what you’re able to collect and what importance [those] data may have depending on the incentives you’re trying to [provide].”

“[Access to these metrics] has led to significant changes in the way that we think and deliver cancer care. We need to think through better how we reduce the burden on reporting from practices, which is a significant issue for reporting quality metrics, while at the same time really focusing on those that [affect] outcomes the most.”

ROOM TO GROW
In terms of the future of health economic outcomes, Wilfong said there is a long road ahead of clinicians in particularly when it comes to seamless integration into daily practice.

“Where I’d like to see us move to is better risk profiling, where instead of taking single tools or single bits of data and thinking about patient care, how do we incorporate a plethora of data points into what patients’ outcomes should be,” he said adding that this will include taking time to thoroughly consider a patient’s risk profile and address their concerns at the point of care. “[We need to take] the patients’ voice into our decision making much more robustly than we do so that we can take all of that data and really truly understand what the trajectory of that patient is.”

REFERENCES
The Most Advanced Cancer Care in Arkansas

The UAMS Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences is the only team in Arkansas providing CAR T-cell therapy to treat multiple myeloma and certain lymphomas and leukemias. We provide the state’s only bone marrow and stem cell transplantation program and the largest number of clinical trials for more cancer types than any provider in the state.

Our world-renowned Myeloma Center is an international leader in the treatment and study of multiple myeloma and related diseases. With more than 25 years of clinical and research excellence, our novel therapy approach results in continually improved survival rates.

With our team of 160+ clinicians and researchers, we’re the team to help your patients beat cancer. To learn more, visit UAMS.Health/Cancer-Services

UAMS Winthrop P. Rockefeller Cancer Institute
449 Jack Stephens Drive,
Little Rock, Arkansas 72205
Patient referrals: 501.686.6080
Tackling the Adverse Effects of Immunotherapy
by IGOR PUZANOV, MD, MSCI, FACP

IMMUNOTHERAPY AGENTS REPRESENT A transformational advance in our ability to treat many cancers. Rather than introducing a therapy that kills both healthy and malignant cells, immunotherapy agents harness the body’s natural ability to recognize and control the invasive cells that can form tumors.

Most patients who receive immunotherapy will experience few, if any, treatment-related adverse effects (AEs). But some patients receiving these treatments can experience serious AEs caused by an overactivation of the immune system and its effects on healthy cells.

It is important for clinicians to identify AEs quickly and assign such toxicities an appropriate grade using the standard Common Terminology Criteria for Adverse Events 5.0 grading system. Based on that grading, treatment should be designed using standard guidelines developed by oncology societies, including the Society for Immunotherapy of Cancer and American Society of Clinical Oncology (ASCO). Most of the toxicities caused by immunotherapy drugs are reversible by using steroid or other immunosuppressive therapies.

It is critical to ensure clinicians recognize and know how to manage these treatment-emergent AEs so patients can seek appropriate medical attention quickly and continue to take advantage of the benefits of immunotherapy.

COMMON AEs OF IMMUNOTHERAPY

Several immunotherapy drugs have been approved by the FDA to treat various types of advanced cancers. Approved immunotherapies include CTLA-4 inhibitor ipilimumab (Yervoy); PD-1 inhibitors pembrolizumab (Keytruda), nivolumab (Opdivo), and cemiplimab (Libtayo); and PD-L1 inhibitors atezolizumab (Tecentriq) and avelumab (Bavencio) (TABLE 1). Immunotherapy AEs can be difficult to identify because they can cause symptoms that are associated with common ailments and infections. Some of these adverse reactions might resemble another medical issue but require a very different course of action. For example, pneumonitis, which a small number of patients on checkpoint inhibitor immunotherapy may experience, can cause some of the same symptoms as viral or bacterial respiratory infection but should be treated with steroids instead of antibiotics. The primary immunotherapy-related AEs patients and clinicians should be aware of include flu-like symptoms, asthenia, arthralgias, and rash. Endocrinopathies such as thyroiditis, hypophysitis, adrenal insufficiency, and type I diabetes must be recognized quickly, as these complications may lead to the need for lifelong hormonal replacement therapy.

There have been reports of inflammation of organs, including pneumonitis, pancreatitis, hepatitis, nephritis, colitis, dermatitis (redness, itchiness, or rash), neuritis, uveitis, and myocarditis. Although myocarditis occurs in fewer than 1% of patients receiving immunotherapy, it is likely the most serious adverse reaction that can occur because of these agents.

Early detection of this potentially fatal AE, which carries a 40% to 50% risk of death, is critical, but there are currently no clear ways to accurately predict or identify this type of immunotherapy-associated toxicity.

I was recently part of a multidisciplinary team at Roswell Park Comprehensive Cancer Center (Roswell Park) that identified troponin, a protein that enters the bloodstream only when the heart is damaged, as an early and reliable predictor of myocarditis in patients with cancer receiving immunotherapy with immune checkpoint inhibitors.

Findings of this retrospective study, which reviewed the records of 1001 patients with cancer who were treated with 1 or more immunotherapy agents at Roswell Park from 2016 to 2020, suggested that weekly troponin monitoring during the first 6 weeks of treatment could help physicians detect this rare but potentially fatal AE of immunotherapy. Any patient showing an elevation in troponin levels or signs of cardiotoxicity, such as angina or arrhythmia, should be referred to a cardio-oncology team for complete evaluation, including electrocardiogram, echocardiogram, or cardiac MRI.

Although immunotherapy-related myocarditis is extremely rare, it occurs with greater frequency and severity when immunotherapy drugs are given in combination, and early recognition is critical. For example, in a multicenter analysis, my colleagues and I identified 2 cases of myocarditis that developed in patients with metastatic melanoma following treatment with a combination of ipilimumab and nivolumab, which are 2 commonly used immune checkpoint inhibitors.

TREATMENT OF IMMUNOTHERAPY AEs

Reduction of immunotherapy-related AEs relies heavily on corticosteroids and other immunomodulatory agents, which should be prescribed to reduce the potential for short-term and long-term complications. It remains unclear whether prophylactic antibiotics should routinely be prescribed to reduce the potential for opportunistic infection in patients receiving steroids. Treatment should be individualized depending on each patient’s medical history, comorbidities, and underlying disease status, as well as the type, number, and severity of AEs.

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**TABLE 1. AEs of FDA-Approved Cancer Immunotherapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Common AEs of any grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Fatigue, diarrhea, increased ALT, hyperglycemia</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Fatigue, rash, hyperglycemia, hypertriglyceridemia</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Fatigue, rash, diarrhea, increased ALT</td>
</tr>
<tr>
<td>Cemiplimab</td>
<td>PD-1</td>
<td>Fatigue, rash, diarrhea, musculoskeletal pain</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Anemia, fatigue, decreased appetite, diarrhea</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Fatigue, lymphopenia, anemia, increased AST</td>
</tr>
</tbody>
</table>

AEs, adverse effects; ALT, alanine transaminase; AST, aspartate aminotransferase.
TABLE 2. Recommended Guidance for CTCAE-Based Cardiovascular AEs Associated With ICI Therapy

Snapshot of guidance on treatment-emergent cardiotoxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>CTCAE description</th>
<th>Guidance</th>
<th>Specialist referral?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abnormal cardiac biomarker testing, including abnormal ECG</td>
<td>Recommend baseline ECG and cardiac biomarker assessment (ie, BNP, troponin) to establish whether there is a notable change during therapy</td>
<td>If abnormal results are detected</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal screening test with mild symptoms</td>
<td>Control cardiac diseases (eg, heart failure, atrial fibrillation)</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Moderately abnormal testing or symptoms with mild activity</td>
<td>BNP &gt;500 pg/ml, troponin &gt;99% institutional normal, new ECG findings</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions</td>
<td>If myocarditis is identified, consider high-dose corticosteroids (1 mg/kg methylprednisolone IV) until improved to grade ≤ 1, then consider at least 4-5 weeks of tapering doses*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AE, adverse effect; BNP, brain natriuretic peptide; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ICI, immune checkpoint inhibitor; IV, intravenous.

*Patients with confirmed myocarditis or reasonable suspicion of myocarditis should receive emergent high-dose corticosteroids. Until data are available to determine when to start corticosteroids in patients with possible myocarditis, this decision should be made on a case-by-case basis. Active, ongoing consultation with a cardiologist should occur to discuss the risk/benefit of continuing ICI therapy, starting corticosteroids, or instituting other cardiac treatments.

**Table 2 continued**

<table>
<thead>
<tr>
<th>Grade</th>
<th>CTCAE description</th>
<th>Guidance</th>
<th>Specialist referral?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td>Consider withholding ICI</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>If a period of stabilization is achieved and definite cardiac toxicity was not identified, it may be reasonable to consider rechallenging the patient with ICI, with heightened monitoring.</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>If confirmed cardiac injury or decompensation, hold ICI therapy until stabilized</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Optimally treat identified cardiac conditions</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Consider corticosteroids if myocarditis suspected*</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Permanently discontinue ICI</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Administer additional supportive treatments, including appropriate treatment of heart failure</td>
<td></td>
</tr>
</tbody>
</table>

**Guidance for Medical Professionals**

Because immunotherapy is a relatively new treatment option, many of these agents have AEs that have not been previously observed. AEs stemming from immunotherapy use can affect the skin, lungs, gastrointestinal and endocrine systems, joints, heart, and other organs. Some of these AEs are just beginning to be described, therefore clinicians need guidance on how to recognize early signs, how to treat AEs, and when to refer a patient to a disease specialist. For this reason, I have been helping to create guidance for medical professionals who care for patients receiving immunotherapy drugs. Along with other experts in this field, I helped write the first consensus guidelines on how to recognize and respond to immunotherapy-related AEs and am contributing to similar resources to be issued by ASCO and the National Comprehensive Cancer Network (Table 2).

Information is key in identifying and managing any AEs of immunotherapy. It is critical for medical professionals to give patients clear written guidance before a course of immunotherapy is started and to keep that flow of information going back and forth during clinic visits and between appointments. When my patients on immunotherapy ask me about possible AEs, I stress that immunotherapy is an incredibly important and effective option for treating many cancers and that AEs are rare. I also strongly encourage my patients to become active participants in their treatment by learning about these possible AEs, monitor for these adverse reactions, and respond to any symptoms that develop. Together, we can help to ensure these new and advanced treatments are as effective as possible.

**REFERENCES**


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“Impact is key in identifying and managing any AEs of immunotherapy. It is critical for medical professionals to give patients clear written guidance before a course of immunotherapy is started and to keep that flow of information going back and forth during clinic visits and between appointments.”

—IGOR PUZANOV, MD, MSCI, FACP
LIBTAYO® (cemiplimab-rwlc)

LIBTAYO® is indicated for the first-line treatment of patients with non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [tumor proportion score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is:

- Locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- Metastatic

NCCN Guidelines® for Non-Small Cell Lung Cancer recommend cemiplimab-rwlc (LIBTAYO) as a Category 1* (preferred) systemic therapy option for advanced NSCLC.

**LIBTAYO significantly EXTENDED SURVIVAL vs platinum-based chemotherapy in EMPOWER-Lung 1**

<table>
<thead>
<tr>
<th>Number of deaths</th>
<th>Reduction in risk of death</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% of patients (108 out of 356 patients) with LIBTAYO</td>
<td>32%</td>
<td>22.1 months (95% CI, 17.7-19.2)</td>
</tr>
<tr>
<td>40% of patients (141 out of 354 patients) with chemotherapy</td>
<td></td>
<td>14.3 months (95% CI, 11.7-19.2)</td>
</tr>
</tbody>
</table>

**Study design**

EMPOWER-Lung 1 was a large, phase 3, randomized, open-label, multicenter study that included patients with locally advanced advanced NSCLC who were not candidates for treatment with definitive concurrent chemoradiation or patients with stage IV disease who received no prior systemic treatment for recurrent or metastatic NSCLC. Key eligibility criteria included PD-L1 expression ≥50% and EGFR PS 0 or 1. Patients with type 1 diabetes mellitus or hypothyroidism only requiring hormone replacement were eligible. Patients with brain metastases that were treated and clinically stable (neurologically returned to baseline) for at least 2 weeks prior to randomization were permitted. Radiological confirmation of stability or response was not required. Patients were excluded if they had EGFR, ALK, or ROS1 aberrations, a medical condition that required systemic immunosuppression, uncontrolled infections with hepatitis B, hepatitis C, or HIV, autoimmune disease that required systemic therapy within 2 years of treatment, and never-smokers.

Patients were randomized 1:1 to receive LIBTAYO 350 mg IV Q3W for up to 108 weeks or investigator’s choice of the following platinum-doublet chemotherapy regimens for 4 to 6 cycles: paclitaxel + cisplatin or carboplatin; gemcitabine + cisplatin or carboplatin; or pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance in patients with nonsquamous histology. Treatment with LIBTAYO continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or for up to 108 weeks. Patients who experienced IRC-assessed RECIST 1.1-defined progressive disease on therapy with LIBTAYO were permitted to continue treatment with LIBTAYO 350 mg Q3W for up to 108 additional weeks, along with the addition of histology-specific chemotherapy for 4 cycles until further progression was observed. Patients who experienced IRC-assessed RECIST 1.1-defined progressive disease on chemotherapy were permitted to receive treatment with LIBTAYO monotherapy until further progression, unacceptable toxicity, or for up to 108 weeks.

The primary efficacy endpoints were OS and PFS. Secondary endpoints included ORR (key), DOR, and safety and tolerability.

**Important Safety Information**

**Warnings and Precautions**

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Please see additional Important Safety Information and Brief Summary of full prescribing information on the following pages.
In an analysis of the subset of patients with advanced NSCLC who had no EGFR, ALK, or ROS1 aberrations and known PD-L1 ≥50% (n=563):

**Overall survival with LIBTAYO vs platinum-based chemotherapy in EMPower-Lung 1**

- Number of deaths: 25% of patients (70 out of 283 patients) with LIBTAYO and 38% of patients (105 out of 280 patients) with chemotherapy.
- **72%** of patients who progressed on platinum-based chemotherapy crossed over to LIBTAYO treatment.

**Clinical safety data**
- **LIBTAYO** was permanently discontinued due to adverse reactions in 6% of patients.
- Adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke, and increased aspartate aminotransferase.
- Serious adverse reactions occurred in 28% of patients receiving LIBTAYO.
- The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

**Important Safety Information (continued)**

**Warnings and Precautions (continued)**

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Early identification and management are essential to ensuring safe use of PD-1/PD-L1—blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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

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

**Immune-mediated pneumonitis:** LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1—blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Return in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
Important Safety Information (continued)

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/ PD-L1—blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN. For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

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

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

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

• Hypophysitis: LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 6.7% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

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

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

• Hyperthyroidism: Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hyperthyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

• Hypothyroidism: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

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

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1—blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.7%). Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of
Important Safety Information (continued)

Warnings and Precautions (continued)

Severe and Fatal Precautions (continued)

Immune-mediated dermatologic adverse reactions: in the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

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

Infusion-related reactions

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

Complications of allogeneic HSCT

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

Embryo-fetal toxicity

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

Adverse Reactions

- In the pooled safety analysis of 810 patients, the most common adverse reactions (≥15%) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea.
- In the pooled safety analysis of 810 patients, the most common Grade 3-4 laboratory abnormalities (≥2%) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Use in Specific Populations

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

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

References:
Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes, initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes mellitus.

Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitated LIBTAYO after symptom improvement; 1 required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

Hypothyroidism: Hypothyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%) adverse reactions. No patient discontinued treatment due to hypothyroidism.

Hypothyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.3% (8/242) of patients with hypothyroidism. Hypothyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hypothyroidism, 2 reinitated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

Hypophysitis: Hypophysitis occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (8%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids led to withholding of LIBTAYO in 1.1% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitated LIBTAYO after symptom improvement; 1 required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

Hypothyroidism: Hypothyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%) adverse reactions. No patient discontinued treatment due to hypothyroidism.

Hypothyroidism led to withholding of LIBTAYO in 0.5% of patients.
Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception to prevent pregnancy when receiving LIBTAYO and for at least 4 months after the last dose. (See Use in Specific Populations (8.1, 8.3)).

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fetal Immune-Mediated Adverse Reactions (see Warnings and Precautions (5.1))
- Infusion-Related Reactions (see Warnings and Precautions (5.2))
- Complications of Allogeneic HSCT (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.

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label, randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=543), or other doses (n=321) mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for ≥ 6 months and 25% were exposed for ≥ 12 months. In this pooled safety population, the most common adverse reactions (≥ 15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were lymphopenia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Non-Small Cell Lung Cancer (NSCLC)

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 (See Clinical Studies (14.3) in the full prescribing information). Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin, gemcitabine plus cisplatin or carboplatin, or pemetrexed plus cisplatin or carboplatin followed by optional maintenance. The median duration of exposure was 27.3 weeks (10 to 118 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22% were exposed for ≥ 12 months.

The safety population characteristics were: median age of 62 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2% of patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 6 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

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, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

6.3 Antibody Testing

Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

6.4 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) in the full prescribing information). There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data).

Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO can have the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

7. USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

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

8.6 Pediatric Use

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

8.7 Pregnancy

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

8.8 Lactation

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its 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 and for at least 4 months after the last dose of LIBTAYO.

8.9 Females and Males of Reproductive Potential

8.10 Contraception

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

8.11 Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.12 Male

No data are available in male patients. Use LIBTAYO with caution in male patients with female partners of reproductive potential.

8.13 Laboratory Abnormalities

Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624 (continued)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO n=355</th>
<th>Chemotherapy n=342</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>3.9</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>2.7</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Increased lactate dehydrogenase</td>
<td>1.8</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>2.1</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v. 4.03

a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624 (continued)

<table>
<thead>
<tr>
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<tr>
<td>Increased blood bilirubin</td>
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<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
The Most Important Thing About a Master Plan Is Not Having One

AS THE DIRECTOR OF 3 centers at Dana-Farber Cancer Institute, a professor of medicine at Harvard Medical School, and head of The Jänne Lab, you might wonder what master plan Pasi A. Jänne, MD, PhD, drafted in his youth to make him so successful. The truth? He never had one. Rather, he’s always done what has felt right by following his intuition and curiosities, a concept that he tries to instill in his fellows to this day.

"So many people want to have a 1-, 2-, and 5-year plan, but it may not work. Sometimes if you’re too rigid and you can’t see it any other way or any other things, there may be opportunities that are missed along the way," Jänne, the 2021 Giants of Cancer Care® award winner for lung cancer, said in an interview.

Born in Helsinki, Finland, and raised in a rural town with a brother 4 years his junior, Jänne was no stranger to the scientific world. His father worked as a biologist, and in 1980, when Jänne was 12, his father’s employer sent the family to the United States. The move was supposed to be temporary, but the family came to enjoy living in New York, New York. Jänne eventually enrolled in Vassar College, a liberal arts school approximately 2 hours north of New York City. Having worked in science labs since high school, Jänne pictured attending a larger university that was known for science. But at Vassar, he was exposed to the college’s highly regarded art history program, an opportunity that likely would not have been as readily available to him at a larger scientific research university.

"I learned how to appreciate art, and now when I travel to major cities, I always try to go to the art museums to see those pieces that I learned about in college in real life," he said.

Following graduation in 1989, Jänne enrolled in a 7-year combined MD/PhD program at the University of Pennsylvania in Philadelphia. Apart from knowing he wanted to pursue medicine and science in some capacity, Jänne was not sure where he wanted to focus. But, guided by his unwavering passion for research and with direction from his PhD mentor, a human geneticist, Jänne pursued a doctorate in human genetics. The decision, coupled with his interest in medicine and prior exposure to hematologists.
and oncologists during his medical rotations, led him to oncology. Jänne felt the discipline would allow him to explore the overlap between science and medicine.

“As I was thinking about fields of medicine, I wanted to think about where the application of genetics in medicine was likely to happen,” he said. “Certainly, hematology/oncology seemed like a reasonable place compared with, for example, cardiology or neurology.”

It was also during graduate school that Jänne met his wife, Karen Cichowski, PhD, now a cancer biologist and head of the Cichowski Lab at Brigham and Women’s Hospital and Harvard Medical School. Upon graduation, Jänne, certain on medicine, began seeking out fast-track residency programs in internal medicine while his wife began applying for postdoctoral positions.

“Jänne explained that his decision to specialize in lung cancer was first influenced by the etiology and multidisciplinary management of the disease. “I was interested in lung cancer as a kind of medical illness because, having just trained in internal medicine, lung cancer was a disease where all disciplines of medicine are involved, and people get sick in very different ways,” he said. Second, but equally as important, Jänne received guidance from Bruce Johnson, MD, the 2018 Giants of Cancer Care award winner for Prevention/Genetics, and his colleague, William Sellers, MD, were conducting first-generation lung cancer sequencing studies with samples from treatment-naive patients who had undergone surgery.

However, because the patients were untreated, investigators couldn’t correlate the presence of EGFR mutations with response. Instead, they noticed that the incidence of EGFR mutations was higher in Asian patients. At the same time, Jänne was analyzing the patients who had outstanding responses to gefitinib, as well as studying model cell lines from patients in the laboratory.

“We knew that clinically, patients responded, but it wasn’t an even distribution, meaning that there were some clinical characteristics that were associated with the response,” Jänne said.

Jänne and his colleagues independently sequenced the EGFR gene from the sensitive and nonsensitive cell lines and realized that the sensitive cell line, H3255, had a sensitizing EGFR L858R mutation—the very same EGFR mutation that Meyerson and his colleagues observed in their patients.

“That was our aha moment, and it was great because I remember this was right [around] when my daughter was born, so I was holding my daughter in one hand [while] we were having a phone call about this [realization],” Jänne said. The next step was identifying the patients who’d had lights-out responses to gefitinib, all of whom were found to have an EGFR mutation.

In June 2004, Jänne and his colleagues published their findings correlating response to gefitinib with EGFR mutations. That same summer, pathologists at Dana-Farber had already begun to establish a first-generation clinical sequencing protocol.

“If patients were found to have an EGFR mutation, we could get them on an EGFR inhibitor,” Jänne said, which also paved the way for the investigation of EGFR inhibitors in the frontline setting, where they are primarily used today.

“[From there], the whole story came together. It came from all these independent pieces, but the mutation was the thread that unified it all,” Jänne said. “I’m not even sure that we fully appreciated the significance of the finding at the time [in terms of] what it would do and how it would change lung cancer and medicine.”

Three years later, Jänne and colleagues published research demonstrating that not only was the loss of response to gefitinib driven by MET amplification, but that inhibition in MET signaling could restore sensitivity to gefitinib, paving the way for further study of resistance mechanisms to both earlier- and next-generation inhibitors.

Now physicians have a range of targetable alterations, including ALK, RET, MET, ROS1, NTRK, and KRAS.

“One of the things that really distinguishes scientists who make an important contribution to our body of scientific information is the ability to make consistent, insightful observations about what is driving the sensitivity and resistance to our therapeutic agents,” Johnson said in an interview with OncologyLive. “The series of observations that Dr Jänne has made consistently over the past 20 years have contributed to how we treat our patients in the clinic.”
Unmasking NETs Requires a Multifaceted Approach to Care

by BRITTANY LOVELY

NETs used to be considered quite rare and it’s one of those diseases where we do not receive that much education on it in medical school or in our training process. So, it’s kind of an unusual, unknown disease, but it affects a lot of individuals,” Liu is surgical director of the Neuroendocrine Institute at Rocky Mountain Cancer Centers in Denver, Colorado.

As a community oncologist with a specialty in NETs, Liu highlighted the most important aspect of the disease: awareness. “The neuroendocrine system is one that no one ever talks about. We talk about the respiratory tract and the digestive tract and the central nervous system and even the endocrine system. But the neuroendocrine system is more like what we call the diffuse system is [one] that no one ever talks about. We [individuals] have mild symptoms [including] abdominal pain, a little flushing here and there, maybe some diarrhea, and [they] come and go in some cases.

We also have different blood tests as well; however, they are not quite as good. Unfortunately, the treatments for irritable bowel syndrome and menopause do not treat cancer and so as the symptoms persist, the disease persists. Thankfully, it’s a slow growing disease in general and individuals can live with it for a long time. It is a very challenging diagnostic dilemma. But once the diagnosis is made, thankfully there is a lot we can do to help patients.

Luckily, we do have good diagnostic techniques to confirm NETs. The easiest one is a CT scan, [which is] quick, standard, lots of individuals can get it, it’s not very expensive, and it provides a survey of the lungs, stomach, and pelvis. That is frequently how we make the diagnosis of NETs by seeing a mass either in the intestines, the pancreas, or the liver.

It is a tough diagnosis to make. [Let’s take an example of] a 50-year-old woman who presents with flushing, a very common symptom for NETs. If that is the situation, a gynecologist may present a diagnosis of menopause. [What if a] patient has persistent diarrhea? A gastroenterologist may prescribe a colonoscopy and results may not show anything but the symptom persists. The gastroenterologist may give a diagnosis of irritable bowel syndrome. You can see how these mild symptoms can very easily be misinterpreted, and the diagnosis of NETs is not made for a long time.

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We also have different blood tests as well; however, they are not quite as good. Unfortunately, [because] NETs are slow growing, and individuals can have them for many years without any symptoms, [they] frequently are diagnosed very late, usually stage IV. Stage III [disease] tends to include spread to the local lymph nodes, but stage IV is when it spreads far, for example to the liver, bones, or lungs.
NETs typically start in the lungs, pancreas, or small intestine, which are the 3 most common points of origin [and] even though it has a reputation for being a very slow disease, it is aggressive in the way that it spreads. Neuroendocrine disease is not benign; it is a highly metastatic disease that can be life-threatening.

**How do you decide whether to pursue looking for NETs?**

We must consider comorbidities and age [at the time of diagnosis], which is usually 60 years, but can be seen in a patient who is age 40 or 50 years. Treatments can be quite varied and include medicines, surgery, special kinds of radiation, and different kinds of therapies for the liver... [We must] take into consideration the overall general health of the patient.

For example, if the patient has many comorbidities, such as diabetes, or a history of stroke, and they are elderly and very frail, maybe the treatment for the neuroendocrine disease needs to take a back seat to something else, because if a patient is going to die, for example due to a stroke or a heart attack, NETs may not be the most life-threatening aspect of their health. But if a patient is quite healthy, they don’t smoke, and are doing well, my goal is always to keep the patient healthy. And our goal, as it should be for everything, is to heal the patient so that they can live a high quality of life. If I can help improve quality of life, that’s always my No. 1 priority.

**What are the typical treatments that you are looking to initiate once a patient has received a diagnosis of NETs?**

Despite neuroendocrine [disease] being a relatively unusual and rare, we have many different types of therapies. And the reason that I encourage patients to see specialists is because choosing the tools in the toolbox can be very challenging. We need to decide what is best for the patient and one tool clinicians forget is surveillance. Then we have other types of medicines, because neuroendocrine [cancer] is a hormonal disease, and one of the unusual things is that NETs may affect blood sugar [and] they may cause pain. And so, getting those hormones under control is very important.

**FIGURE. Treatment Pathways for Patients With Metastatic or Unresectable NETs**

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic disease</td>
<td>Metastatic or unresectable</td>
</tr>
<tr>
<td>Surgery</td>
<td>¹⁷⁷Lu-Dotatate</td>
</tr>
<tr>
<td>Observation</td>
<td></td>
</tr>
<tr>
<td>Systemic treatment if widespread</td>
<td></td>
</tr>
<tr>
<td>Progressive and/or symptomatic disease</td>
<td></td>
</tr>
<tr>
<td>Systemic treatment if widespread</td>
<td></td>
</tr>
<tr>
<td>Nonpancreatic</td>
<td></td>
</tr>
<tr>
<td>SSTR positive</td>
<td>Somatostatin Everolimus CAPTEM</td>
</tr>
<tr>
<td>SSTR negative</td>
<td>Somatostatin Everolimus</td>
</tr>
</tbody>
</table>

CAPTEM, capecitabine plus temozolomide; NETs, neuroendocrine tumors; SSTR, somatostatin receptor.

**Treatment Snapshot: NETs in the Clinic**

NEUROENDOCRINE NEOPLASMS OR neuroendocrine tumors (NETs) present across varying tumor sites in a broad range of grades and in patients with varying functional statuses. No consensus or for the optimal treatment of NETs is available, with treatment pathways determined in large part by the individual characteristics of the patient upon disease diagnosis (FIGURE).

Diagnostic via somatostatin receptor (SSTR) imaging is recommended to confirm NETs using one of the following agents:
- ⁶⁸Ga-Dotatate positron emission tomography (PET)
- ⁶⁴Cu-Dotatate PET
- ⁶⁸Ga-Dotatoc PET

Further, there are 6 key patient and tumor characteristics to consider when determining treatment options, as follows:
- Extent and burden of disease (localized vs metastatic/unresectable; liver dominant vs widely metastatic; low volume vs high volume)
- Hormone status (functional vs nonfunctional)
- Grade (low vs high)
- Pace of growth (stable vs progressive)
- Primary site (pancreatic vs nonpancreatic)
- SSTR status (positive vs negative)

But there’s no question that up front one of the most powerful therapies that we have for neuroendocrine disease is surgery. If we can remove a lot of the bulk of the tumor, we can remove a fair amount of the hormone burden, which is not usually the case for other cancers.

However, a lot of the times the disease goes to the liver, and we can use embolization. Additionally, one of the most exciting therapies we have is called PRRT, or peptide receptor radionuclide therapy, which combines hormonal therapy with radiation that goes straight to the tumor and the
radiation treatment [as delivered] from the inside out. It’s very effective in helping to control the disease. It is not a cure, but it can help patients with symptoms and can help slow down the growth of their tumors.

**Q** Are there any other unmet messages you would like to convey to the community oncologist regarding NETs?

**Liao** I always say, have a buddy. Have a friend who specializes in neuroendocrine disease who you can talk to. I should stress that I am community physician, so I understand what it is to be out there working with patients in their community. I’ve seen 2000 cases of NETs and I’ve learned how vastly complicated the disease really is. What I always tell clinicians is, don’t be shy, order all the tests, gather all the information up front so you can have all the correct data and can make the best decision.

One of the problems I see frequently as a specialist who receives referrals is that sometimes the patient did not have a complete workup. [In some cases] the clinicians jumped to [one type of] surgery, when in fact maybe you could have done a little better surgery if you had more information. Or in other cases, the wrong therapy was administered because the pathology was misinterpreted. There are lots of different ways that the devil is in the details.

I always encourage my colleagues across the United States [to see this as] a team effort. I am happy that the patient always has their [primary oncologist] at home because they get their treatments, shots, and their scans [locally] and they don’t have to fly to Denver, Colorado to see me every single month; that would be ridiculous. If we can work together, and I can share some of my experience with you, we can come up with the best plan for the patient. That is always the best that we can do.

I don’t know everything about brain cancer, bone cancer, or bladder cancer but I know a lot about neuroendocrine cancer. And so, I am happy to rely on my colleagues who really specialize in those other things.

There is one other thing I do want to share, neuroendocrine disease really isn’t that rare, and there is a lot we can do to help patients. Unfortunately, the information is not readily available, which means that individuals need to advocate for themselves—either the patient needs to advocate, or the physician needs to advocate—get the right tests, seek second opinions, don’t worry about having to travel because you might have to do that.

Luckily, if anything has come from the COVID-19 pandemic, it is that we do a lot more telemedicine now. Reach out and see [whether] some of the experts in the United States would be willing to see you through telemedicine and review your case. A lot of the time, a physician at home can conduct the physical exam and with the advanced scans that we have, I can see right into their bodies. So, most of the time, they just need me to think about the case.

Think about getting a second opinion, think about working with a specialist, make sure you get a comfortable team around you. If they say something is impossible, that might not always be true.

**REFERENCES**


**FROM THE EXPERTS**

Leading experts in neuroendocrine tumors (NETs) speak with OncologyLive® on the latest data, and trends in care that are shaping the treatment landscape for patients. Watch and read more by scanning the QR codes or visiting OncLive.com.

**Liao on Novel Targets in NETs**

“In terms of other novel classes of systemic therapy, [investigators are] using novel targets, such as SSTR2. PEN-221 is an antibody-drug conjugate that targets SSTR2. There are other examples of drugs that link the SSTR2 to CD3 like a bispecific engager. Those are new classes of drugs with new mechanisms of action, and we have seen some very preliminary data [with those agents]. We’re excited to see what the clinical trials show in terms of what benefits they will provide for our patients.”

**Reidy-Lagunes Unpacks Recent Updates in NETs**

“The biggest challenge is that we don’t know what is the optimal sequencing strategy. Is what is the best second- and third-line treatment? Oftentimes 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 who has low-volume disease and is asymptomatic, you may be able to just watch.”

**Kunz on Tailoring Therapies for NETs**

“Tailoring treatments to patients with NETs and continuing to develop more effective therapies are important elements of care for this patient population. However, the caveat is that many patients with well-differentiated NETs can live for many years with metastatic disease, so it is important that the risks associated with the therapeutic intervention don’t outweigh the risks of the disease. Moreover, it is important that therapies elicit disease control and tumor shrinkage while still allowing patients to maintain a good quality of life.”

Chih-Yi (Andy) Liao, MD

Diane Reidy-Lagunes, MD

Pamela Kunz, MD
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Superagonists Pull IL-15 Into Focus in Oncology Care

by ONCLIVE® STAFF

FOLLOWING IN THE FOOTSTEPS of the cytokine interleukin (IL)-2, IL-15 affords investigators similar qualities as a target without the associated toxicities of its immunotherapeutic predecessor. Because IL-15 represents a potential potent immune modulator, leveraging its ability to activate effector T and natural killer (NK) cells may rely on the development of immune cytokines with additional antibodies to enhance antibody-dependent cellular cytotoxicity. 2

IL-15 and IL-2 activate downstream JAK/STAT signaling pathways through shared β and γ receptor subunits; however, distinctions between IL-2 and IL-15 become more evident in adaptive immune response and their role in the immunomodulation of T and NK cells in the tumor microenvironment (FIGURE). 2 IL-15 has demonstrated similar receptor binding, biologic activity, and signaling as IL-2, but without the adverse effect (AE) profile, including the induction of severe capillary leak syndrome. 1-2

One of the shortcomings with IL-15, however, is the short half-life because of its small molecular size. Investigators sought to optimize IL-15 with the development of fusion proteins with IL-15Ra bound by flexible linkers that enhance the affinity for IL-15Rβ. This circumvents the need for dendritic cells expressing the subunit receptors for IL-15 to be in proximity for maximum efficacy. 1

Investigational superagonists have demonstrated preclinical effects in murine models including increased half-life from 7 to 20 hours, increased IL-15 potency, and serum stability, with detectability in patient serum up to 7 days after subcutaneous injection. Further, restricted tumor growth and improved median overall survival were also observed in breast and colon cancer tumors, with improved efficacy observed when combined with anti-CTLA or anti-PD-L1 therapies. In terms of hematologic models, when IL-15 was combined with anti-CD20 antibodies, NK cell responses were improved in murine B cell lymphomas. 1

APPLICATIONS ACROSS SOLID TUMORS

Investigators have observed preclinical efficacy of IL-15–directed therapies in combination with other targeted therapies has paved the way for investigators to evaluate IL-15 superagonists in phase 1 and phase 2 trials. For more on recent advances observed in solid tumors, see the SIDEBAR.

N-803

N-803 (Anktiva) is a first-in-class IL-15 superagonist consisting of 3 key structural components: the cytokine (IL-15N72D), the cytokine fusion (IL-15Ra), and the antibody (IgG1 Fc). Specifically, the cytokine and antibody work in tandem to proliferate endogenous NK cells/CD8-positive T cells without inducing T-regulatory stimulation in the tumor microenvironment. Additionally, the IgG1 Fc has demonstrated the ability increase the agent’s half-life and increase honing to the CD16 receptors expressed on NK cells and macrophages. 3

Bladder Cancer Sees Marked Results

Preliminary data from the phase 2 QUILT 3.055 trial (NCT03228667) demonstrated the tolerability of the IL-15 superagonist across multiple cohorts of patients who received N-803 in combination immune checkpoint inhibitors (ICls) after prior treatment with ICls. 3 Specifically, among the 140 patients who received therapy, serious treatment-related AEs (TRAEs) were observed in 8% of patients, including respiratory failure in 1 patient that was grade 5 and attributed to N-803 and the ICI. 3

Investigators also reported that compared with standard chemotherapy-containing regimens, the investigative approach had lower rates of AEs. In terms of efficacy, 49% of individuals responded to N-803 treatment.


FIGURE. Interaction of IL-2 and IL-15 With Receptors and Down Signaling Pathways

IL-2 and IL-15 share receptor subunits (IL-2/15Rβ) that trigger the downstream activation of the JAK/STAT pathways and may also mediate the PI3K/AKY pathway with subsequent mTOR activation. IL-2 and IL-15 mediate several similar functions on immune modulation including the promotion, proliferation, and activation of CD4-positive and CD8-positive T cells. Additionally, IL-2 and IL-15 generate and promote the persistence of NK cells.

IL-2

n Interleukin

NK, natural killer.

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THE ADDITION OF SOT101, an interleukin (IL)-2/IL-15 Rβγ superagonist, to pembrolizumab (Keytruda) generated a clinical benefit and encouraging safety data in patients with advanced solid tumors, according to data presented at the American Association for Cancer Research (AACR) 2022 Annual Meeting.1

Investigators of the phase 2 AURELIO-03 dose-escalation trial (NCT05256381) observed complete response (CR) in 1 patient, partial response (PR) in 4 patients, and confirmed stable disease (SD) of at least 50 weeks in 5 patients receiving this combination. Twelve out of 16 patients with at least 1 tumor assessment experienced clinical benefit, including those who were relapsed/refractory to immune checkpoint blockade (ICB). “SOT101 is a fusion protein containing IL-15 and the Sushi+ domain of IL-15Rα. It mimics a high-affinity binding of IL-15 trans-presented to its βγ receptor at the synapse. Therefore, it doesn’t require dendritic cells to trans-present IL-15,” Stéphane Champiat, MD, PhD, assistant professor in the Department of Drug Development Gustave Roussy Cancer Campus in Villejuif, France, said in his presentation.

“Compared [with] IL-2, it does not activate [regulatory T cells] due to the fact the IL-15 does not bind to IL-2Rα. Therefore, SOT101 may have a better efficacy over [other] IL-2/IL-15 compounds because of a strong and well-balanced induction of both innate and adaptive immunity by activating T cells or NK [natural killer] cells.”

The primary end points of the open-label, single-arm, multicenter AURELIO-03 study were safety, tolerability, recommended phase 2 dose (RP2D), preliminary efficacy, pharmacokinetics, and pharmacodynamics. SOT101 was given subcutaneously on days 1, 2, 8, and 9 in combination with pembrolizumab at 200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity. Standard 3 + 3 escalation was used, with 3 patients receiving 1.5 μg/kg of SOT101, 3 receiving 3.0 μg/kg, 7 receiving 6.0 μg/kg, 3 receiving 9.0 μg/kg, and 5 receiving 12.0 μg/kg.

The maximum-tolerated dose of SOT101 was not reached; the RP2D was determined to be 12 μg/kg. Investigators concluded there was no additive toxicity because the adverse events (AEs) seen with the combination were comparable to the toxicity profile of SOT101 and pembrolizumab used as monotherapy.

Safety data were available for 21 patients at 5 dose levels of SOT101 ranging from 1.5 to 12 μg/kg. Most AEs were grade 2 or lower, with the most common being pyrexia, chills, and vomiting. Grade 3/4 treatment-emergent AEs included lymphopenia in 7 patients, alanine aminotransferase/aspartate aminotransferase (ALT/AST) and pyrexia in 2 patients each, and neutropenia, anemia, and cytokine release syndrome in 1 patient each.

One patient had dose-limiting toxicity of grade 2 cytokine release syndrome, with grade 2 hypotension and fever, after the first administration of SOT101 at 6 μg/kg. However, this resolved after 6 days, and the patient continued at 3 μg/kg. No other dose-limiting toxicities were observed at higher dose levels. Due to grade 3 ALT/AST, 1 patient on 1.5 μg/kg discontinued study treatment, and the AE resolved within 12 days after discontinuation. There was no incidence of treatment-related death or vascular leak syndrome.

At the data cutoff of February 3, 2022, there was 1 confirmed CR in a patient with mesothelioma at a dose level of 9 μg/kg of SOT101. Among multiple dose levels, there were 3 confirmed PRs and 1 unconfirmed PR in patients with medullary thyroid gland cancer not pretreated with ICB, ICB-refractory skin squamous cell carcinoma (SCC), and ICB-relapsed skin melanoma and melanoma of the cervix. SD was confirmed in 5 patients and unconfirmed in 2 others with anal SCC, gastric cancer, cervix adenocarcinoma, liver cancer, and colorectal cancer across dose levels. The longest duration of response was more than 40 weeks.

To be eligible for enrollment, adult patients had to be refractory or intolerant to existing therapies and needed to have confirmed metastatic or unrespectable solid tumors. Additionally, adequate renal, hepatic, and hematological function and an ECOG performance status of 0 or 1 were required.

In the safety population, the median age was 62 years, and 11 patients were female. Fourteen had an ECOG performance status of 0. Patients had a median of 2 prior lines of therapy, although 10 patients had 3 or more lines before entering this study. Eleven patients had prior ICB treatment. The most common disease types on the trial were colorectal cancer (n = 3), melanoma (n = 3), gastric cancer (n = 2), anal SCC (n = 2), and mesothelioma (n = 2).

In a presentation of the data, Champiat highlighted 2 case studies. The first was a 49-year-old woman with anal SCC who was ICB-refractory and had SD for 52 weeks. The patient received a diagnosis in August 2019 and received 5-fluorouracil, leucovorin, and oxaliplatin in the first line, retifanilimab in the second line, and SOT101 at 1.5 μg/kg with pembrolizumab as third-line therapy.

“There was a dramatic increase of CD8-positive infiltrate and PD-L1 expression, and it triggered an infiltration of NK cells,” Champiat said. “[This] suggests that SOT101 in combination with pembrolizumab can induce an increase in immune cell infiltration in ICB-refractory tumors.”

In the second case study, a 74-year-old woman with skin SCC had a best response of PR. She received a diagnosis in 2016, underwent 22 surgeries, and received cemiplimab-rwlc (Libtayo) for 4 cycles before developing primary resistance. In the AURELIO-03 trial, she was given 6 μg/kg of SOT101. After 4 cycles, she had a PR in her target lesions and fluctuating new lesions were appearing and disappearing, for significant clinical response. The patient has had more than 50 weeks of treatment and is still receiving therapy.

Champiat concluded that based on the encouraging efficacy signals observed in these heavily pretreated patients, SOT101 plus pembrolizumab will be investigated in the phase 2 AURELIO-04 trial (NCT05256381). This will be an open-label, single-arm, multicenter trial for patients with advanced or refractory solid tumors to further evaluate efficacy and safety.2

REFERENCES
on the trial had stable disease (SD), with 36% having SD more than 2 months and 16% having SD more than 6 months. Overall, 13 patients had a partial response to therapy.3

N-803 received a breakthrough therapy designation from the FDA in December 2019 for the treatment of patients with BCG-unresponsive non-muscle invasive bladder cancer following promising results from a phase 1/2 study (NCT02138734) of the agent in combination with BCG.4

Data from the ongoing phase 2/3 QUILT-3.032 trial (NCT03022829) of the combination have met the primary end point. In updated data from cohort A of the trial presented at the 2021 American Urological Association Annual Meeting, the complete response (CR) rate was 72% (95% CI, 61%-81%) among the 81 patients enrolled.5 Additionally, investigators reported that patients who had a response had a 58.6% (95% CI, 43.1%-71.2%) probability of maintaining a CR for at least 12 months. At a median follow-up of 20.4 months, the median duration of CR was 19.9 months (95% CI, 7.8-not reached). As of data cutoff of May 19, 2021, 30% of patients had a durable response at 18 months.5

Investigators aimed to curb the incidence of patients progressing to radical cystectomy. In the trial, 85% of patients were able to avoid cystectomy following administration of 50 mg of BCG plus 400 mg of intravesical N-803 weekly for 6 weeks. Of note, the patient population was heavily pretreated, with patients having received a median of 12 prior BCG instillations and a median of 5 prior transurethral resections of bladder tumors, as well as 42% of patients having received prior treatment with chemotherapy in addition to BCG.5

In terms of safety, the combination was well tolerated, with no grade 4/5 AEs. Two patients experienced grade 3 TRAEs (uroinary tract infection and arthralgia). The most frequent grade 1/2 AEs were dysuria (22%), hematuria (16%), and pollakiuria (19%).5

Combinations Fuel Progress in Pancreatic Cancer

Pancreatic cancer is notoriously difficult to treat. Investigators in the phase 2 QUILT-88 trial (NCT04390399) are hoping to elicit the activation of a patient’s entire immune system with a unique combination of low-dose chemoradiation, cytokine-induced NK-cell and T-cell activation, and PD-L1-targeted high-affinity NK cell (t-taNK) infusion. The QUILT-88 trial leverages N-803 in combination with standard-of-care chemotherapy, aldoxorubicin hydrochloride (a type II DNA topoisomerase inhibitor), stereotactic body radiation therapy, and an off-the-shelf PD-L1 t-taNK.

The study protocol was designed to evaluate the treatment across 3 cohorts stratified by line of therapy (first, second, and third or later), with a primary end point of progression-free survival. Data from the cohort of 61 patients who received therapy in the third or later line were presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.6

The median overall survival (OS) in the overall cohort was 5.8 months (95% CI, 3.9-6.9). For those who received treatment with the investigational combination in the third line, the median OS was 6.8 months (95% CI, 5.0-9.8), which investigators noted more than doubled the median OS vs historical standards after second-line therapies. TRAEs were uncommon and occurred in 8% of patients, with no treatment-related deaths reported. Additionally, investigators noted that all treatments were administered in an outpatient setting.4

Forward-Looking Prospects Include Lung and Breast Cancers

In patients with stage IIIB or IV non–small-cell lung cancer (NSCLC), investigators hope to build on early synergistic effects of N-803 plus PD-1 inhibitors.7 Investigators of the phase 3 QUILT 2.023 trial (NCT03520686) will assess N-803 in combination with anti- PD-1 standard-of-care regimens pembrolizumab (Keytruda) with or without chemotherapy vs standard of care alone.8 Additionally, in October 2021, the combination of N-803 and pembrolizumab was selected for investigation as part of the Lung Cancer Master Protocol, or Lung-MAP.9 The precision medicine trial is a collaboration between the National Cancer Institute, Northwestern Oncology Group Cancer Research, Friends of Cancer Research, the Foundation for the National Institutes of Health, and private companies. Investigators of the phase 2/3 trial (NCT05096663) will evaluate the safety and efficacy of the investigational combination vs investigator’s choice of docetaxel, gemcitabine, or pemtrexed in combination with ramucirumab (Cyramza). The trial is expected to enroll approximately 478 patients with advanced NSCLC.10

Investigators also seek to capitalize on retreatment efficacy of N-803 by including it as a component of a chemoimmunotherapy backbone in the ongoing QUILT 3.058 trial (NCT04927884) in combination with sacituzumab goviecan-hzly (Trodelvy) for patients with triple-negative breast cancer who have had at least 2 prior therapies. N-803 will administered subcutaneously at 15 μg/kg with cyclophosphamide (25 mg) and PD-L1 t-taNK (approximately 2 × 10⁹).11

REFERENCES
A LEADER IN CAR T-CELL IMMUNOTHERAPY

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New Treatment Options Are in Play for Relapsed/Refractory DLBCL

by CHRISTINA T. LOGUIDICE

UP TO 40% OF patients with diffuse large B-cell lymphoma (DLBCL) are refractory to or relapse after first-line treatment. Although CD20 once served as a promising target, patients with DLBCL often developed resistance or did not respond to targeted frontline treatments, which led investigators to uncover other pan-B cell targets in the first- and later-line settings. The likelihood of cure decreases with each relapse, and disease refractory to second- or later-line treatment lines is associated with a survival of less than 5 years. For most patients, high-dose chemotherapy and stem cell transplantation remain the standard of care in the second line. However, treatment options are expanding with CD19-directed chimeric antigen receptor (CAR) T-cell therapies and monoclonal antibodies (mAbs), several of which have been approved by the FDA in the past 5 years.

“We’ve gone from a disease where the curve kept dropping and patients kept relapsing and dying of their cancer to where we’re curing at least a subset,” Jason Westin, MD, said during a recent OncLive Peer Exchange®. “It’s very gratifying to see these novel approaches begin to bear fruit, and the idea of adding our amazing new targeted therapies to 1970s chemotherapy. I’m hopeful that we can start having novel-novel combinations in the front line and I’m quite intrigued by the potential for moving CAR T cells to even earlier lines.”

Westin was joined by a panel of hematology cancer experts to discuss CD19-directed CAR T-cell therapies, including clinical and real-world data for these agents. The panel also discussed several CD19-directed mAbs that are helping to move treatment in the second line away from chemotherapy, a shift that they hope will eventually reach the frontline setting.

“Years ago, [Dr Westin] was proposing chemotherapy-free approaches in frontline therapy of DLBCL,” Grzegorz S. Nowakowski, MD, said. “At that time this was heretical, and all of us had a fast heartbeat just listening to him talk about it. It’s very rewarding to see that the mindset is changing. There’s an ongoing discussion of chemotherapy-free approaches in frontline management of large cell lymphoma—how we can select the right population, how we can design those studies, and how we can slowly go away from R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone] therapy. That’s exciting to see because, ultimately, replacing this fairly antiquated therapy would be a goal if we can achieve it.”

CAR T-CELL THERAPIES

Three CD19-directed CAR T-cell therapies are approved by the FDA for patients with relapsed
or refractory (R/R) DLBCL: axicabtagene ciloleucel (axi-cel; Yescarta), tisagenlecleucel (tisa-cel; Kymriah), and lisocabtagene maraleucel (liso-cel; Breyanzi). These agents all bind to CD19 via a monoclonal antibody called FMC63 but have some differences in how they are produced (eg, standard retrovirus vs lentivirus), their underlying mechanisms, and their approved indications.2

“All 3 were desperately needed by patients to bring forward a therapy with enough capacity for individual cell manufacturing and personalized care across what was estimated to be 10,000 to 15,000 patients with R/R DLBCL annually,” David Miklos, MD, PhD, said (TABLE 1).3-6

Axicel
Axi-cel received FDA approval in April 2022 for adult patients with LBCL who are refractory to first-line chemomunotherapy or who experience disease relapse within 12 months of first-line chemomunotherapy, making it the first CAR T-cell therapy to receive a second-line treatment indication. It is also approved after at least 2 lines of systemic therapy.8

Approval in the second-line setting was based on data from the phase 3 ZUMA-7 trial (NCT03391466), which randomly assigned 359 patients to receive axi-cel (n = 180) or standard care (n = 179). After a median follow-up of approximately 25 months, the median event-free survival (EFS) was 8.3 months (95% CI, 4.5-18.3) in the axi-cel group and 2.0 months (95% CI, 1.6-2.8) in the standard-care group, with a 24-month EFS rate of 41% and 16%, respectively (HR, 0.40; 95% CI, 0.31-0.51; P < .0001). The percentage of responders was 1.66 times as high in the axi-cel group as in the standard-care group at 83% (95% CI, 77%-88%) vs 50% (95% CI, 43%-58%), respectively (P < .0001), with a complete response (CR) observed in 65 vs 32% of patients. An interim analysis estimated the OS rate at 2 years to be 61% in the axi-cel group vs 52% in the standard care group.9

Initial approval of axi-cel as a third- or subsequent-line treatment was based on data from the phase 2 ZUMA-1 study (NCT02348216), which showed an objective response rate (ORR) of 72% with a CR rate of 51% (95% CI, 41%-62%).2 Long-term overall survival (OS) and safety data from ZUMA-1, which now has more than 5 years of follow-up, were reported at the 63rd American Society of Hematology Annual Meeting and Exposition (2021 ASH).8 The 5-year OS rate was 42.6% (95% CI, 32.8%-51.9%); among those alive at 5 years, 92% received no additional treatment following axi-cel.9

“One thing I’d like to highlight from the long-term follow-up from ZUMA-1 [and other studies] is that we’re seeing what I consider to be a plateau, so I use the word cure when I talk to my patients,” Westin said. “When patients are more than 6 to 12 months out, we don’t have a lot of events that occur at those late time points.”

Tisa-cel
Tisa-cel received FDA approval in May 2018 for adult patients with R/R DLBCL previously treated with at least 2 lines of systemic therapy based on data from the phase 2 JULIET trial (NCT02445248).10 In the study, 93 patients received a tisa-cel infusion.10 The best overall response rate was 52% (95% CI, 41%-62%), with CRs in 40% of patients and partial responses (PRs) in 12% of patients. Twelve months following the initial response, the relapse-free survival rate was an estimated 65% in the total population and 79% among patients with a CR.

Investigators are exploring the efficacy of tisa-cel in the second-line setting in the ongoing phase 3 BELINDA trial (NCT03570892).11 A total of 322 patients were randomly assigned to tisa-cel with optional bridging therapy (ie, tisa-cel group) or salvage chemotherapy and autologous stem-cell transplantation (ASCT; ie, standard-care group). A response occurred in 46.3% of patients in the tisa-cel group and 42.5% of patients in the standard-care group; however, the trial did not meet its primary end point of EFS, which was 3 months in both groups (HR, 1.07; 95% CI, 0.82-1.40; P = .61).12

The panelists noted 2 key challenges that may have led to the suboptimal results seen in the BELINDA trial—a longer product manufacturing time with tisa-cel vs the other CD19-directed...
CAR T-cell therapies and the use of bridging therapies, which made it difficult to tease out how much was attributable to tisa-cel. “On the BELINDA trial, the median time to infusion was 52 days,” Westin said. “That comes down to that late time point and the need to get 2 different types of platinum chemotherapy in the standard-care arm. Everybody was apheresed, but the products weren’t made until an individual had shown response to the first type of platinum chemotherapy, hence the need to give another one, because the long time frame to make the product started after the 6 weeks of chemotherapy.” He noted that 12% of patients in the CAR T-cell arm received 2 different types of bridging therapy. “This is a very complicated trial design,” he said.

Liso-cel

Liso-cel received FDA approval in February 2021 for adult patients with R/R DLBCL previously treated with at least 2 lines of systemic therapy based on data from the phase 1 TRANSCEND-NHL-001 study (NCT02631044). In the study, 269 patients received at least 1 dose of liso-cel.

Among the 256 who were efficacy evaluable, the ORR was 73% (95% CI, 66.8%-78.0%), with 53% of patients experiencing a CR (95% CI, 46.8%-59.4%) and 20% having a PR (95% CI, 14.9%-24.9%).

The median time to first response was 1 month, which is also the time frame in which most patients achieved their best response. At a median of 3 months, investigators observed that patients with an initial PR achieved a CR (n = 28), and a small proportion of patients who had an initial response of stable disease achieved a CR or PR (n = 7). Of the patients who achieved a response, 60% had remission lasting at least 6 months and 55% had remission lasting at least 12 months. The median OS was 21 months (95% CI, 13.3-not reached [NR]), with 75% of patients alive at 6 months and 58% alive at 12 months.

Two-year follow-up data from TRANSCEND-NHL-001 were reported at 2021 ASH. At 24 months, the probabilities of continued response, PFS, and OS were 49.5% (95% CI, 41.4%-57.0%), 40.6% (95% CI, 34.0%-47.2%), and 50.5% (95% CI, 44.1%-56.3%), respectively.

In the phase 3 TRANSFORM trial (NCT03575331) investigators evaluated the efficacy of liso-cel in the second-line setting. Individuals were randomly assigned to receive liso-cel or standard of care. The median EFS was 10.1 months in the liso-cel arm vs 2.3 months in the standard-care arm (HR, 0.349; P < .0001), and the median PFS was 14.8 months vs 5.7 months, respectively (HR, 0.406; P = .0001). In the liso-cel arm, 66% of patients achieved a CR compared with 39% of patients in the standard-care arm (P < .0001). OS data were immature at the time of the analysis, which had a median follow-up of 6.2 months (range, 0.9-20.0), but were trending toward favoring liso-cel (HR, 0.509; 95% CI, 0.258-1.004; P = .0257).

Miklos noted that, as shown with axi-cel in the ZUMA-7 trial, results from the TRANSFORM study again showed an improved CR rate in the second vs third line. “That might be due to fresher T-cells, more fit immune systems, and less exposure to prior chemotherapy—arguing again that these therapies, which are good in the third line, might be even better in the second line,” he said. “In fact, when we look at the publications, we’re all struck by how if you [received] the ASCT and if you got the CAR T-cell [therapy], there was a remarkable plateau in the patients who received both therapies.”

Emerging Real-World Data

Recently, a considerable amount of real-world data for CAR T-cell therapy has emerged. For example, investigators of a small single-center Italian study who treated 18 patients with axi-cel and 12 with tisa-cel reported best ORR and CR rates of 73.3% and 40% among the entire population, respectively, showing the high response rates of these agents maintained outside of a clinical trial. When available CAR T-cell treatments have been compared, no significant differences in efficacy or safety have been observed. In a matching-adjusted indirect comparison of tisa-cel and liso-cel, investigators found no differences in OS, PFS, or CR.

“What we’ve seen are remarkably striking similar outcomes from the clinical trials, both in terms of the efficacy—the long-term PFS and OS—as well as the toxicity profile in an increasingly diverse population in terms of their comorbidities and functional status,” Westin said. He emphasized that CD19-directed CAR T-cell therapies

### TABLE 2. Outcomes for Approved Anti-CD19 mAbs for DLBCL<sup>19,21</sup>

<table>
<thead>
<tr>
<th>Tafasitamab</th>
<th>Tafasitamab (n = 71)</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Best ORR (95% CI)</td>
<td>55% (43%-67%)</td>
</tr>
<tr>
<td>CR</td>
<td>37%</td>
</tr>
<tr>
<td>PR</td>
<td>18%</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>21.7 (0-24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Loncastuximab tesirine</th>
<th>Loncastuximab tesirine (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Best ORR (95% CI)</td>
<td>48.3% (39%-66.7%)</td>
</tr>
<tr>
<td>CR</td>
<td>24.1%</td>
</tr>
<tr>
<td>PR</td>
<td>24.1%</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>10.3 (6.9-NR)</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response; OS, overall survival.}<sup>22</sup>
by tafasitamab monotherapy in patients with R/R DLBCL ineligible for ASCT. The ORR was 57.5%, with 40.0% being CRs and 17.5% being PRs. The median duration of response was 43.9 months (95% CI, 26.1-NR), the median OS was 33.5 months (95% CI, 18.3-NR), and the median PFS was 11.6 months (95% CI, 6.3-45.7).

More recently, at 2021 ASH data were presented from RE-MIND2 (NCT04697160), a retrospective cohort study comparing outcomes from L-MIND with matched patients who were treated with National Comprehensive Cancer Network/European Society for Medical Oncology-recommended therapies. Tafasitamab plus lenalidomide improved survival outcomes vs polatuzumab vedotin-piq (Polivy) plus bendamustine/rituximab (Rituxan) and rituximab plus lenalidomide in closely matched patient populations. The results were comparable to what we have seen with CAR T-cell [therapies], Nowakowski said. “The number of patients in the CAR T-cell comparison is limited. We’d like to see more data and more mature data. But this prototype targeting CD19 in the right patients is important. You can do it in many different ways, and antibody IMiD [immunomodulatory imide drug] combinations could be one of those ways.”

**Loncastuximab tesirine**

Loncastuximab tesirine-iplv (Zynlonta) is a CD19-directed antibody and alkylating agent conjugate. It received accelerated FDA approval in April 2021 for adult patients with R/R DBCL after at least 2 lines of systemic therapy. Approval was based on data from the phase 2, open-label, single-arm LOTIS-2 trial (NCT03589469). In the study, 145 patients received at least 1 dose of loncastuximab tesirine. The study included patients at high risk for a poor prognosis, such as those with double- or triple-hit, transformed, or primary refractory DLBCL. The ORR was 48.3% (95% CI, 39.9-56.7) with CRs and PRs each occurring in approximately 24% of patients.

“What I found particularly exciting about this study is that it included a fair share of patients who were post-CAR T-cell therapy, and in the signal of activity in those patients, although number was limited, it showed that the response rate was maintained, which is very encouraging,” Nowakowski said, adding that a benefit of mAbs is that it can be combined with other therapies to improve their efficacy. “This is that whole revolution of different concepts and ways that we can now sequence or combine those therapies to improve outcomes of patients with R/R DLBCL,” Nowakowski said.

**REFERENCES**

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