New Programs Unlock Patient Access to Oncology Care

PEER EXCHANGE
Combinations Gain Momentum as First-line Treatments for Unresectable HEPATOCELLULAR CARCINOMA

Hotspot ESR1 Mutations Drive Tumor Stickiness in Metastatic Endocrine-Resistant BREAST CANCER

CONFERENCE HIGHLIGHTS
7th Annual School of Gastrointestinal Oncology®
Leading Experts Provide Updates Across GASTROINTESTINAL MALIGNANCIES

CLINICAL TRIAL IN FOCUS
Jose Conejo-Garcia, MD, PhD, Discusses Cellular Therapy Approaches in OVARIAN CANCER

Molecular Approaches May Increase Responsiveness to Immunotherapy for Patients With Metastatic MELANOMA

By Alan J. Tackett, PhD; and Nathan L. Avaritt, PhD

Scan the QR code to watch the first-of-its-kind online program for health care professionals, by health care professionals.
For your patient with non-metastatic castration-resistant prostate cancer (nmCRPC)

HELP HIM LIVE FOR WHAT HE LOVES

MEN LIVED 2X LONGER WITHOUT CANCER SPREADING1,2
40.4 months vs 18.4 months for ADT alone
HR: 0.41; 95% CI: 0.34-0.50; P<0.0001 (intent-to-treat).

REDUCED RISK OF DEATH BY NEARLY A THIRD1,3
31% reduction in the risk of death vs ADT alone
Secondary endpoint: HR: 0.69; 95% CI: 0.53-0.88; P=0.003. Medians not estimable.

PROVIDED THE RELIEF OF AN EXTRA 15 MONTHS WITHOUT PAIN PROGRESSION1,3*
40.3 months vs 25.4 months for ADT alone
Secondary endpoint: HR: 0.65; 95% CI: 0.53-0.79; P<0.0001.

**CHOOSE NUBEQA® 1st FOR EXTENDED SURVIVAL.**
NUBEQAHCP.COM

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

**IMPORTANT SAFETY INFORMATION**

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

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

**Drug Interactions**
Effect of Other Drugs on NUBEQA – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

**NUBEQA® (darolutamide)** 300 mg tablets

**Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.**

**Study design**
The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤10 months. 1509 patients were randomized 2:1 to 600 mg NUBEQA twice daily (n=955) or placebo (n=554). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, 99mTc bone scan by BICR; unacceptable toxicity, or withdrawal. ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; BPI-SF=Brief Pain Inventory Short Form; PSA=prostate-specific antigen; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging.
NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

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

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

2 CONTRAINDICATIONS
None.

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

Adverse events with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Use in Specified Populations (8.1, 8.3, 8.5)).

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

5.3 Females and Males of Reproductive Potential
Contraception
Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Use in Specific Populations (8.5)).

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

ARMS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (mCRPC), in this study, patients received either NUBEQA at a dose of 600 mg or a placebo, twice a day. All patients in the ARMS study received a concurrent gonadotropin-releasing hormone (GnRH) analog or a bilateral orchectomy. The median duration of exposure was 14.6 months (range 0.1 to 44.3 months) in patients who received NUBEQA.

Overall, adverse events occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in > 1% of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.7% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.1%), and pulmonary embolism (0.1%) for NUBEQA.

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

Table 1 shows adverse reactions in ARMS reported in the NUBEQA arm with a 5% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARMS study.

Table 1: Adverse Reactions in ARMS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=54)</th>
<th>Placebo (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Grade 3+</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Laboratory Test Abnormalities in ARMS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=54)</th>
<th>Placebo (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Grade 3+</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARMS study.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on NUBEQA

Concomitant use of NUBEQA with a combination of P-gp and strong/moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity (see Clinical Pharmacology (12.2)). Avoid concurrent use of NUBEQA with a combination of P-gp and strong/moderate CYP3A4 inducers. Concomitant use of P-gp and strong CYP3A4 Inducers

Concomitant use of NUBEQA with a combination of P-gp and strong CYP3A4 Inducer decreases darolutamide exposure (see Clinical Pharmacology (12.2)) which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed (see Dosage and Administration (2.2)).

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptide (OATP) 1B1 and OATP1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates (see Clinical Pharmacology (12.2)), which may increase the risk of BCRP substrate-related toxicities.

Avoid concurrent use with drugs that are BCRP substrates wherever possible. If used together, monitor patients more frequently for adverse reactions and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 and OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA (see Clinical Pharmacology (12.2)).

Embryo-Fetal Toxicity

Adverse effects and fetal malformations were observed in animal studies. NUBEQA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (13.1, 13.2)).

Pediatric Use

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

Geriatric Use

Of the 954 patients who received NUBEQA in ARMS, 86% of patients were 65 years and over, and 49% were 75 years and over. There were no overall differences in safety or efficacy observed between these patients and younger patients.

Renal Impairment

Patients with severe renal impairment (eGFR 15–29 ml/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended (see Dosage and Administration (2.4) and Clinical Pharmacology (12.2)). No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 ml/min/1.73 m²). The effect of end stage renal disease (eGFR ≤15 ml/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended (see Dosage and Administration (2.4) and Clinical Pharmacology (12.2)). No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on darolutamide pharmacokinetics is unknown.

OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1100 mg. No dose limiting toxicities were observed with this dose.

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

In the event of an intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted. Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo comet assay mouse micronucleus assay and the Comet assay in the liver and bone marrow of rats. Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats, no alterations in weight gain and spermatid counts up to 39 weeks, tubular dilatation of testes, hyperemia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats at 8.6 times the human exposure based on AUC and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT CONSENTING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information) before treatment and administration.

Informed patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

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

Informed patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose (see Dosage and Administration (2.2)).

Embryo-Fetal Toxicity

Advise patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy (see Use in Specific Populations (8.1, 8.3, 8.5)).

Adverse Events with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3, 8.5)).

Integrity

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

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References:
Your Link to Everything Oncology

OncLive® is proud to partner with the leading cancer care centers across the United States. We collaborate on educational content so oncology professionals will have the resources and information they need to improve patient outcomes.

Scan the QR code with your mobile device to discover the reach and visibility of our Strategic Alliance Partnership network.
Innovative strategies to improve patient access to oncology care aim to circumvent the hurdles facing both community and institutional practitioners: getting patients to the right providers at the right time. Two pilot programs featured in this month’s cover story provide foundational methods for evaluating standard processes and implementing new approaches to elicit referrals and increase retention.

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Publisher's Note

Connecting Patients With the Right Care at the Right Time

BUILDING BRIDGES BETWEEN patients, community clinics, and institutions is an ongoing and complicated component of oncology care. Coordinating records, awareness of new innovations in care, providing appropriate resources to the right care teams, and circumventing barriers to diagnosis represent a few of the multilevel hurdles facing providers and patients.

However, innovations in accelerated communication tactics between patients and care teams have laid the foundation for instituting new approaches to access and retention. In our cover story, leaders from 2 OncLive® strategic alliance partners—Yale Cancer Center and Moffit Cancer Center—discuss how their institutions are meeting patients and referring clinicians where they are to open the doors for access to care. “There is no silver bullet for access. We really need to be doing things that have an upstream effect and [can change] the system,” Timothy A. Price, MBA, FACHE, director of patient access at Moffit Cancer Center said in a presentation at the National Comprehensive Cancer Center 2022 Annual Meeting.

The 2 models are both patient-centric pilot programs aimed at getting patients connected with a provider who has knowledge of their disease state within 24 hours of their initial diagnosis or suspected cancer. The programs provide a high-level overview of internal changes that may need review to accommodate referrals and identify key areas of unmet need for both the referring clinician and the intake institution.

As Matthew L. Meyerson, MD, PhD, this issue’s featured Giant of Cancer Care® winner in prevention and genetics, said, many people might be surprised by the social nature of the science field and how many ideas develop not as an independent "eureka" moment but as part of a conversation. “A lot of that scientific progress is thinking together and discovering together. Maybe that’s a piece an individual hasn’t fully understood, that isn’t always fully captured,” Meyerson said in an interview at the time of his award.

The efforts undertaken at our partner institutions highlight a small sampling of the teamwork driving change across oncology care. Over the past 5 years, the recognition that therapies introduced into clinical practice frequently may not be evaluated in the patients who would most benefit from them has helped spur an effort to broaden clinical trial eligibility criteria. For example, discrepancies persist between populations included in clinical trials for FDA approvals and real-world patient populations. Slight progress has been made with efforts from the American Society of Clinical Oncology and the Friends of Cancer Research have proposed protocol amendments. The FDA has implemented some changes in clinical trial guidance documents as a result.

As more changes come to light, OncLive®’s Disparities in Cancer Care condition center will be updated to reflect the latest clinical news and exclusive insights from leaders in the field. Visit onclive.com/clinical/disparities-in-cancer-care for more.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®
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 1,3

**Study design**

**EMPower-Lung** was a large, phase 3, randomized, open-label, multicenter study that included patients with locally 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 ECOG 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.1,4

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.1,5

The primary efficacy endpoints were OS and PFS. Secondary endpoints included ORR (key), DOR, and safety and tolerability.1,4

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.1

**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.
The EMPower-Lung 1 study was designed to enroll patients with PD-L1 ≥50%.

- A total of 710 patients were enrolled and randomized. For some patients, it was later determined that PD-L1 biomarker testing was not conducted according to the instructions for use, and required retesting.
- An analysis was conducted in a subset of patients with known PD-L1 ≥50% (n=563). The analysis excluded 91 patients from the overall population whose PD-L1 status was unknown because their tumors could not be retested, and 56 patients from the overall population who had <50% PD-L1 expression (LIBTAYO is not indicated in patients with <50% PD-L1 expression).

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. 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.

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

Warnings and Precautions (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, 57% (2/3) remained on systemic corticosteroids. Adrenal insufficiency was not resolved in any patient at the time of data cutoff

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

• Thyroid disorders: LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of 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 (0.5%). 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 83.3% 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 of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to 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 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of
PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT. Intervene promptly. Consider the benefit versus risks of treatment with an intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause). These complications may occur despite intensity conditioning, and steroid-requiring febrile syndrome (without an infectious cause).

Fatal and other serious complications can occur in patients who receive PD-1/PD-L1–blocking antibodies. 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.

**Important Safety Information (continued)**

**Warnings and Precautions (continued)**

**Immune-mediated dermatologic adverse reactions (continued):** 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.

- **Cardiovascular:** Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis

- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

- **Endocrine:** Hypoparathyroidism

- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

**Infusion-related reactions**

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

**Complications of allogeneic HSCT**

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

**Embryo-fetal toxicity**

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

**Adverse Reactions**

- In the pooled safety analysis of 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:**

1. LIBTAYO (cemiplimab-rwc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.


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LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use

**INDICATIONS AND USAGE**

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 [see Dosage and Administration (2.1) in the full prescribing information], with no EGFR, ALK or ROS1 alterations, and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing information of the immune system to control cancer. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also occur after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be 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 to initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. In general, immune-mediated adverse reactions are reversible when the agent is discontinued. Withhold the agent unless a clear etiology is indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. If serious and persistent, potentially fatal immune-mediated reactions may include:

- Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.
- Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient.

Systemic corticosteroids were not required in any patient with hyperthyroidism. Thyrotoxicosis had not resolved in any patient at the time of data cut-off.

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%) adverse reactions. No patient discontinued treatment due to hyperthyroidism.

Hyperthyroidism led to withholding of LIBTAYO in 0.3% of patients. Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients re-initiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hyperthyroidism: Hyperthyroidism occurred in 7.0% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hyperthyroidism led to permanent discontinuation of LIBTAYO in 0.1% patient. Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%) adverse reactions. No patient discontinued treatment due to thyroiditis.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with an oral hypoglycemic agent or insulin as clinically indicated. Withhold or permanently discontinue 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. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immun-mediated Nephritis with Renal Dysfunction

Immun-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO 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 for nephritis, 2 reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immun-mediated Dermatologic Adverse Reactions

In patients with advanced NSCLC receiving PD-1/PD-L1 blocking antibodies. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated dermatologic adverse reactions treated with PD-1/PD-L1 blocking antibodies can include:

- Skin eruptions: Hyperthyroidism, the definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated dermatologic adverse reactions treated with PD-1/PD-L1 blocking antibodies can include:
- Immune-Mediated Nephritis with Renal Dysfunction

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, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory 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, esophagitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Other (Hematologic/Immunologic): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, lactic acidosis, rhabdomyolysis

**ADVERSE REACTIONS**

**Hypersensitivity**

Hypersensitivity occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) and Grade 3 (0.1%) adverse reactions. Hypersensitivity 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) patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cut-off.

**Thyroid Disorders**

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hypothyroidism. Initiate hormone replacement or medical management of hypothyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Thyroiditis: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued treatment due to hypothyroidism.

Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued treatment due to hypophysitis.

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 cut-off.
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 and death of the 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 [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 Fatal 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, 132 patients with Advanced BCC, 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=343), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg 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 (≥5%) were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

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=350</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>3.5</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>3.2</td>
<td>1.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>2.4</td>
<td>0.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>2.1</td>
<td>0.3</td>
<td>2.1</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.

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.

Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc antibodies was 2.2% using an electrochemiluminescent (ECL) bridging immunos assay. 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.

7 USE IN SPECIFIC POPULATIONS

7.1 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. Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has 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.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

7.2 Lactation

Risk Summary

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 breastfeeding children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8 Female and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 72 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 219 patients with mCSCC or iCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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The Saga of Regional Therapy in the Treatment of Ovarian Cancer

by MAURIE MARKMAN, MD

ONE MIGHT REASON THAT the natural progression of cancer clinical trials would dictate that successful early-stage investigative efforts would culminate in the initiation of randomized phase 3 studies to ultimately define a role for a novel approach in disease management.

Although this scenario certainly occurs and has been responsible over the past several decades for the establishment of increasingly effective antineoplastic strategies, for a variety of reasons a large percentage of cancer therapeutics have never been subjected to the rigors of phase 3 testing. One reason for this is that there may not be a regulatory requirement to conduct such studies, for example, with innovative surgical techniques. Another reason may be that the time, effort, cost, and patient resource requirement mandated to initiate and complete randomized studies is simply not practical.

Further, practitioners involved in a particular clinical domain may feel it is not necessary to address certain highly relevant questions in a randomized study. This may be because their clinical experience and training permit them to know the answer in the absence of actual evidence-based data. This phenomenon might at least partially explain the peculiar circumstance under which the role of neoadjuvant chemotherapy in ovarian cancer management has been examined in randomized trials outside the United States, but no study to date has been conducted by the gynecologic oncology community in this country to help provide a definitive answer to this question.1

This commentary addresses what is, essentially, the opposite situation, in which despite numerous well-designed and conducted randomized trials a definitive answer to the role of a very specific approach to disease management remains quite unclear. There is likely no better example of this conundrum than in the discussions of the optimal role for the regional delivery of cytotoxic chemotherapy, specifically platinum agents, in the treatment of patients with ovarian cancer.

TACKLING QUESTIONS IN OVARIAN CANCER

The concept of regional drug administration in ovarian cancer is remarkably simple and was initially proposed and investigated more than 40 years ago.2 It has been reported that greater exposure of ovarian cancer cells to drugs with known activity in the malignancy (eg, cisplatin, carboplatin, doxorubicin, paclitaxel, 5-fluorouracil) can be safely accomplished with systemic delivery results in increased cytotoxicity.3 However, phase 1 and pharmacokinetic studies have revealed that enhanced exposure can be safely achieved following intraperitoneal drug delivery. For example, for cisplatin and carboplatin, drug concentrations 10 to 20 times greater are measured in the peritoneal cavity when the regional route is employed compared with concentrations observed within the systemic compartment following intravenous administration. For paclitaxel, the concentration difference is 1000-fold.3

Data from multiple phase 2 trials have shown that patients who failed to achieve a surgically documented complete response to platinum-based systemic therapy can achieve this clinical state following the delivery of either cisplatin or carboplatin via the intraperitoneal route.3

Nearly 30 years ago, investigators working with National Cancer Institute (NCI)-supported cooperative group networks initiated several phase 3 randomized trials examining regional drug delivery in the management of ovarian cancer. Their aim was to evaluate the role of consecutive cisplatin-based frontline chemotherapy following initial surgical cytoreduction.3 These efforts revealed the feasibility of the intraperitoneal delivery strategy and strong evidence of a survival benefit compared with systemic cisplatin-based drug administration.3 The results led the NCI to issue a clinical announcement informing the clinical oncology community of the outcome of these several strongly evidence-based studies in January 2006.4

Unfortunately, despite the trial results and the guidance of the NCI, controversy surrounded regional cisplatin delivery in the frontline management of advanced ovarian cancer and major objections to its use continued. Concerns included peritoneal toxicity associated with the agents and the presence of indwelling intraperitoneal catheters.1 In addition, during this multiyear period carboplatin almost completely replaced cisplatin as the platinum agent of choice for systemic treatment of ovarian cancer. The transition was based on evidence of a more favorable toxicity profile which included less emesis, and neuropathy, but no difference in survival outcomes. This change in the standard of care in ovarian cancer treatment served to magnify differences in the systemic adverse effects between carboplatin-based systemic therapy and cisplatin-based intraperitoneal drug delivery.
In addition, although rarely openly discussed, there was a striking differential in the positive financial effect on individual practices and oncology centers associated with the administration of antineoplastic drugs vs the relatively poor compensation for the time and effort required to manage intraperitoneal catheters and their complications.

**PROGRESS STALLS IN TRIAL PROTOCOL**

To emphasize the absence of general support of evidence-based data, the most recently reported United States cooperative group phase 3 study (NCT00951496) again compared with what is still considered “experimental” regional delivery with a systemic control arm. This protocol was designed despite prior data revealing the survival superiority associated with regional treatment. Results of the study failed to confirm a survival benefit with intraperitoneal drug delivery. However, for unclear reasons, this study unfortunately did not include an experimental intraperitoneal arm of cisplatin dosed at 100 mg/m²—the approach employed in 3 previous trials and which demonstrated a survival benefit. Instead, investigators elected to administer an unproved dosing regimen of regional cisplatin at 75 mg/m². In addition, all patients in this trial received bevacizumab (Avastin).

What can we conclude from this 40-year experience? Is it that the dose of cisplatin for frontline regional drug delivery needs to be 100 mg/m² (and not lower)? That the administration of frontline bevacizumab overcomes the inferiority of systemic platinum-based therapy compared with regional administration and if the anti-angiogenic agent is employed intraperitoneal platinum delivery is not required? Maybe it is a combination of these 2 factors. Or perhaps the last randomized trial is an outlier compared with the published results from the previous 3 and should not be considered definitive. Finally, could we conclude that regional chemotherapy is not worth the time, effort, and cost, despite the existing evidence-based data?

At the recent Society of Gynecologic Oncology 2022 Annual Meeting on Women’s Cancer investigators from Japan reported the preliminary results of a randomized phase 3 trial (UMIN000003670) that compared regional with systemic delivery of carboplatin without bevacizumab for the frontline chemotherapeutic treatment of ovarian cancer. Results demonstrated a median 3-month improvement in progression-free survival (23.5 months vs 20.7 months; HR, 0.83; P = .041) associated with the intraperitoneal approach.

What should the gynecologic oncology community do with these data? Start another trial to further explore regional drug delivery, or simply ignore the findings?

**REFERENCES**


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**BEHIND THE SCIENCE**

Rare Alterations May Unearth New Treatments for CRC

Investigators have primarily focused on KRAS mutational status to guide therapeutic development in colorectal cancer (CRC), according to Michael J. Overman, MD, of The University of Texas MD Anderson Cancer Center in Houston. However, he said over the years research has expanded to also consider BRAF and HER2 alterations, as well as prognostic factors such as mismatch repair deficiency. Many of these alterations are now included for testing in CRC. Overman pointed out that the field is moving to incorporate rare genomic alterations within gene fusions to guide treatment decisions and recommended that these be considered for testing.

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**DEEP DIVE**

Closing the Gap on Disparities in Clinical Trials

Disparities in care and outcomes for Black patients with cancer have been an ongoing hurdle. Efforts such as diversifying clinical trials to reflect real-world populations may provide a solution, according to Ozuru O. Ukoha, MD, of the John H. Stroger Jr Hospital of Cook County in Chicago, Illinois. For example, Ukoha cited disparities among patients with results of one study assessing clinical cancer enrollment rates by race demonstrating that Black patients represented 3.1% of study populations compared with 76.3% White patients, 18.3% Asian patients, and 6.1% Hispanic patients.

🔗 TO WATCH, VISIT bit.ly/3rHnRIA.

**INSIDE THE PRACTICE**

Minimally Invasive Surgery, Sentinel Lymph Node Biopsy Advance Care for Endometrial Cancer

Integrating minimally invasive surgery into the treatment paradigm for endometrial cancer has significantly decreased postoperative healing time for patients, according to Ami P. Vaidya, MD, of the John Theurer Cancer Center in Hackensack, New Jersey. She said patient testimonials, as well as clinical data, have demonstrated that minimally invasive surgery decreases postoperative pain, time spent in the hospital, and recovery time overall. Additionally, sentinel lymph node biopsy has been a significant advancement in the field of endometrial cancer.

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Third Bevacizumab Biosimilar Is Authorized for Multiple Indications

The FDA has approved bevacizumab-maly (Alymsys), a biosimilar of bevacizumab (Avastin) developed by mAbxience. This regulatory decision makes this the third bevacizumab biosimilar to receive authorization in the United States.

The VEGF inhibitor is indicated for the treatment of patients with the following: frontline or second-line metastatic colorectal cancer (mCRC) in combination with intravenous fluorouracil-based chemotherapy; second-line mCRC in those who have progressed on a frontline bevacizumab product-containing regimen in combination with fluoropyrimidine/irinotecan-based or fluoropyrimidine/oxaliplatin-based chemotherapy; frontline non-small cell lung cancer in combination with carboplatin and paclitaxel; recurrent glioblastoma; metastatic renal cell carcinoma in combination with interferon alfa; persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan; and epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel.

Notably, bevacizumab-maly is not approved for use as adjuvant treatment in patients with colon cancer.

TO READ MORE, VISIT bit.ly/3rF3sUw

Trastuzumab Deruxtecan Receives Priority Review for NSCLC

The supplemental biologics license application for fam-trastuzumab deruxtecan-nxki (Enhertu) for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 mutation and who have received a prior systemic therapy, has been granted priority review by the FDA. The regulatory agency is expected to decide on the application during the third quarter of 2022.

The decision was made after updated overall survival data from the phase 3 UNITY-CLL trial (NCT02612311) demonstrated an increasing imbalance in survival in favor of the control arm comprised of obinutuzumab (Gazyva) plus chlorambucil. The company also announced the voluntary withdrawal of umbralisib for the approved indications of adult patients with marginal zone lymphoma who have previously received at least 1 anti-CD20–based regimen and for adult patients with follicular lymphoma who previously received at least 3 systemic therapies.

In the phase 1 study, trastuzumab deruxtecan elicited an overall response rate (ORR) of 72.7% among the 11 evaluable patients. The median progression-free survival (PFS) was 11.3 months (95% CI, 8.1-14.3). In DESTINY-Lung01, the antibody-drug conjugate elicited an ORR of 54.9% (95% CI, 44.2%-65.4%) among the 91 evaluable patients. The median PFS was 8.2 months (95% CI, 6.0-11.9) and the median overall survival was 17.8 months (95% CI, 13.8-22.1).

TO READ MORE, VISIT bit.ly/3rG9Lam

Pending Applications for U2 in CLL, SLL Are Voluntarily Withdrawn

The pending biologics license application and supplemental new drug application seeking the approval of the combination of ublituximab plus umbralisib (Ukoniq; U2) in adult patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) has been voluntarily withdrawn by TG Therapeutics, Inc.

The decision was made after updated overall survival data from the phase 3 UNITY-CLL trial (NCT02612311) demonstrated an increasing imbalance in survival in favor of the control arm comprised of obinutuzumab (Gazyva) plus chlorambucil. The company also announced the voluntary withdrawal of umbralisib for the approved indications of adult patients with marginal zone lymphoma who have previously received at least 1 anti-CD20–based regimen and for adult patients with follicular lymphoma who previously received at least 3 systemic therapies.

TO READ MORE, VISIT bit.ly/3jLNAv7

ODAC Supports Use of Randomized Data for PI3K Inhibitor Approvals in Hematologic Cancers

In a 16 to 0 vote, with 1 abstention, the FDA’s Oncologic Drugs Advisory Committee (ODAC) voted in support of basing future approvals for PI3K inhibitors on data from randomized clinical trials rather than single-arm trials.

Three PI3K inhibitors are approved by the FDA in hematologic malignancies based on single-arm data: idelalisib (Zydelig) in combination with rituximab (Rituxan) for relapsed chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); copanlisib (Aliqopa) for patients with relapsed follicular lymphoma who have received at least 2 prior systemic therapies; and duvelisib (Copiktra) for those with relapsed/refractory CLL or SLL who have received at least 2 prior therapies. Prior to withdrawal, the approval of umbralisib (Ukoniq) was also based on single-arm data.

All 4 drugs demonstrated durable overall response rates or improvements in progression-free survival. However, 6 postmarketing randomized controlled trials have shown a potential detriment in overall survival and serious adverse effects.

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Pembrolizumab Monotherapy Adds Option in MSI-H/dMMR Endometrial Cancer

by Kyle Doherty

On March 21, 2022, the FDA approved the humanized monoclonal anti–PD-1 antibody pembrolizumab (Keytruda) for the treatment of patients with advanced endometrial cancer that is microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) and who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.1

“This approval gives these patients an option beyond chemotherapy,” David M. O’Malley, MD, said in an interview with OncologyLive®. “In the past, chemotherapy was quite limited in its response rate and the duration of responses was only 3 to 4 months. With [this] recent update, we see response rates of 46%.”

If you get a response, the chance that response lasts [at least] 3 years is approximately two-thirds. These are durable responses; we may actually be talking about curative intent in patients with recurrent uterine cancer who are MSI-H or dMMR.”

O’Malley is a professor in the Department of Obstetrics and Gynecology at The Ohio State University College of Medicine and the director of the Division of Gynecologic Oncology at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University Comprehensive Cancer Center in Columbus.

The approval was based on data from the phase 2, multicenter, nonrandomized KEYNOTE-158 (NCT02628067) trial, which showed that the overall response rate (ORR) was 46% (95% CI, 35%-56%), including a 12% complete response (CR) rate, among 90 patients with advanced MSI-H or dMMR endometrial cancer. Notably, the median duration of response (DOR) was not reached (NR; range, 2.9-55.7).2

“In the past, the options were quite limited in patients with recurrent uterine cancer, and there was no differentiating MSI-H or dMMR,” O’Malley said. “This is a great step into personalized medicine [and] really using the molecular changes within tumors to help us differentiate care and treatments.” O’Malley noted that patients with mismatch repair–deficient or MSI-stable disease should not receive single-agent pembrolizumab. “Those patients have an option of pembrolizumab [plus] lenvatinib [Lenvima],” he said. “It’s very important that we prescribe the proper therapies specifically to those patients with MSI-H or dMMR [disease].”

Safety and Efficacy Outcomes in KEYNOTE-158
Cohort D of KEYNOTE-158 was open to patients with endometrial carcinoma; cohort K enrolled patients with advanced solid tumors that were MSI-H or dMMR. Eligible patients had an ECOG performance status of 1 or less, adequate organ function, and were at least age 18 years. Patients with an immunodeficiency diagnosis, active autoimmune disease requiring systemic therapy within 2 years, or who had been treated with a monoclonal antibody or investigational drug prior to the study were not included.3

In total, 11 patients from cohort D and 79 patients from cohort K were included in the analysis. Patients were treated with intravenous pembrolizumab 200 mg every 3 weeks for approximately 2 years or until unacceptable toxicity or progressive disease. Tumor imaging was performed every 9 weeks for the first year of the study and survival was assessed every 12 weeks. Retreatment with pembrolizumab was offered to those who achieved a CR, a partial response, or stable disease prior to discontinuation.

The primary end point was ORR per RECIST 1.1 criteria assessed by independent central radiologic review. Secondary end points consisted of DOR, progression-free survival (PFS), overall survival (OS), and safety.

Most patients had an ECOG performance status of 1 (61%), had received prior radiation therapy (68%), and had prior surgery (87%). Only 1 patient was treatment-naïve, 51% had 1 prior line of therapy, 22% had 2 prior lines, and 26% had 3 or more lines of prior therapy.

Additional results from the trial showed that 68% of patients had a response that lasted at least 1 year and 44% experienced a response lasting at least 2 years.2 Investigators of the study concluded that the response rate elicited from pembrolizumab in KEYNOTE-158 was especially robust when compared with second-line cytotoxic therapies.3

In an analysis of patients who had at least 1 dose of pembrolizumab administered at least 24 weeks prior to data cutoff (n=79), the median PFS was 13.1 months (95% CI, 4.3-34.4). The 12-month, 24-month, 36-month, and 48-month PFS rates were 51%, 41%, 37%, and 37%, respectively. The median OS was NR (95% CI, 27.2-NR) and the 12-month, 24-month, 36-month, and 48-month PFS rates were 69%, 64%, 60%, and 60%, respectively. In a subgroup analysis stratified by prior lines of therapy, the ORRs were 53% (95% CI, 36%-69%) and 44% (95% CI, 28%-60%) among patients who received 1 previous line of therapy and at least 2 lines of prior therapy, respectively.3

Regarding safety, no adverse effects (AEs) that led to death were reported. Most patients (76%) experienced a treatment-related AE (TRAE) of any grade. Grade 3/4 TRAEs occurred in 12% of patients and 7% of AEs led to treatment discontinuation.2,3

Common TRAEs of any grade included pruritus (24%), fatigue (21%), diarrhea (16%), arthralgia (14%), and nausea (14%). Immune-mediated AEs and/or infusion reactions of any grade occurred in 28% of patients and consisted of hypothyroidism (14%) and hyperthyroidism (8%), among others. Grade 3/4 immune-mediated AEs and/or infusion reactions were less common, occurring 7% of the time.

“The next steps [in this field] are so exciting,” O’Malley concluded. “We have multiple first-line trials, [one of] which is looking at patients with early-stage disease who are at an intermediate risk of recurrence, combining pembrolizumab with radiation [NCT04214067]. Other trials [will] look at patients who are dMMR or MSI-H and treat them with pembrolizumab vs the standard therapy of carboplatin and paclitaxel. We may be replacing the cytotoxic agents with a single immune therapy. The future is bright for our patients with uterine cancer, thanks to immune therapies.”

References

For more with David M. O’Malley, MD, scan the QR code or visit bit.ly/37w2fI6.
FDA grants approval to pembrolizumab (Keytruda) monotherapy for patients with advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) as determined by an FDA-approved test, and who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation.

**Mechanism of action**
- Pembrolizumab, a monoclonal antibody, blocks the PD-1 receptor’s interaction with PD-L1 and PD-L2. This process leads to the PD-1 pathway-mediated inhibition of the immune response, which includes the antitumor immune response.

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

**Dose**
- 200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months

**Company:** Merck

**PIVOTAL CLINICAL TRIAL**
KEYNOTE-158 (NCT02628067) was a multicenter, nonrandomized, open-label, multicohort trial of pembrolizumab at 200 mg every 3 weeks in patients with advanced solid tumors. Patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma were evaluated in cohorts D and K. MSI and dMMR tumor status were evaluated using polymerase chain reaction and immunohistochemistry, respectively.

**Efficacy results in the Keynote-158 trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>46% (35%-56%)</td>
</tr>
<tr>
<td>CR</td>
<td>12%</td>
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<tr>
<td>PR</td>
<td>33%</td>
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<table>
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<tr>
<th>Responders (n = 41)</th>
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<tbody>
<tr>
<td>Median DOR, months (range)</td>
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<tr>
<td>DOR ≥ 12 months</td>
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<tr>
<td>DOR ≥ 24 months</td>
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</tbody>
</table>

**Warnings and precautions**
- Immune-mediated reactions
- Infusion-related reactions
- Complications of allogeneic hematopoietic stem cell transplantation
- Embryo-fetal toxicity

**Commonly reported adverse effects in Keynote-158**

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Pembrolizumab (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24%</td>
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<tr>
<td>Fatigue</td>
<td>2%</td>
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<tr>
<td>Diarrhea</td>
<td>16%</td>
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<tr>
<td>Arthralgia</td>
<td>14%</td>
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<tr>
<td>Nausea</td>
<td>14%</td>
</tr>
<tr>
<td>Rash</td>
<td>11%</td>
</tr>
</tbody>
</table>

**Immune-mediated adverse effects**
- Hypothyroidism | 14% |
- Hyperthyroidism | 8% |
- Infusion reactions | 4% |

**Median sum of target lesions measurable at baseline (range)**

70.9 mm (11.8-282.8)

**References**
New Programs Unlock Patient Access to Oncology Care

by BRITTANY LOVELY

STRATEGIES FOR IMPROVING CANCER care through the development of novel agents, improving personalized medicine, and prevention of disease have revolutionized the oncology landscape over the past several decades. However, a hurdle remains for community and institutional practitioners: to the right providers at the right time.

"Access is a multifaceted construct. It’s not just about the onboarding process or the amount of time that it takes to get that first appointment. It also ensures that the patient can reach a live person when they make a phone call, that they can be seen in a convenient location by a clinician who is an expert in their specific disease, that they can access information about their diagnosis that’s readily available, and be able to afford their care," Sarah Mougalian, MD, said during the 2022 National Comprehensive Cancer Network (NCCN) Annual Conference. She added that treatment should not only be prompt, but also have seamless transitions from the first appointment through every phase of the cancer care continuum. Mougalian is chief ambulatory officer at Yale Cancer Center/Smilow Cancer Hospital and an associate professor of medicine in medical oncology at Yale School of Medicine in New Haven, Connecticut.

Sustainable care following the first point of contact the management of logistics of care affects both the patient and the provider. “The moment that one has a diagnosis [of cancer], they are overcome with a sense of fear and urgency," Christie Pratt, MA, DHSc, said on a panel at the 2022 NCCN Annual Conference. "At that moment both patients and their loved ones need help. It’s about more than just getting them to the best care. It’s deeper than that,” Pratt, is the senior director of Moffitt Medical Group at Moffitt Cancer Center in Tampa, Florida.

Data from a recent meta-analysis of mortality rates across the most common cancer types—bladder, breast, colon, rectum, lung, cervix, and head and neck—demonstrated that delays of 4 weeks or more in cancer treatment initiation were associated with increased risk of death.2 Hazard ratios for delays in systemic treatments had significant associations with delays of 4 weeks in neoadjuvant treatment of bladder cancer (HR, 1.24; 95% CI, 1.03-1.50) and adjuvant treatment of breast cancer (HR, 1.09; 95% CI, 1.07-1.11). Additionally, a 13% increased risk of death was associated with a 4-week delay in adjuvant systemic treatment for patients with colorectal cancer.2 Radiotherapy delays in head and neck cancer (HR, 1.09; 95% CI, 1.05-1.14) and cervical cancer (HR, 1.23; 95% CI, 1.00-1.50) were deemed significant.2

Investigators cited patient, disease, and system factors as key contributors to delays in care. The most cited reasons being workups and specialist consultations. To alleviate the burden of even one of these factors could significantly improve delays in treatment.2

Mougalian and Pratt presented 2 initiatives to improve new patient access to cancer care at Yale Cancer Center/Smilow Cancer Hospital and Moffitt Cancer Center, respectively.1 The programs focused on systemic hurdles, namely reducing delays for patient appointments with disease specialists.

WAITING IS THE WORST PART

Developing a system with a patient-centric focus, investigators at Yale Cancer Center initiated a pilot program to offer patients next day access to care following a diagnosis of cancer. Mougalian and her colleagues began with 2 subspecialty clinics at the institution—breast and gynecologic oncology. “We want it to be easy [for the patient following their] initial consultation to self-refer [and] for the scheduling process to be efficient,” Mougalian said. “We want the patient to be able to see a provider who is expert in their diagnosis in a timely fashion or institutional goal is within 5
patients accepting the appointment. More patients (900) were eligible for next day visits with 12% of patients accepting the appointment. In an analysis between August 2021 and January 2022, these rates dropped from 27% to 20%, respectively.

Among the entire population of patients seen 900 were eligible for next day visits with 12% of patients accepting the appointment. More patients with breast cancer (17%) accepted next day visits than those who received a diagnosis of gynecologic cancer (9%).

The median time to first visit was measured at 2 time points: December 2019 through February 2020, and December 2020 through February 2021. The median time to next visit in the first year was 13 days vs 9 days in the second year. Mougalian stressed the importance of care team coordination through the process. “For providers who refer to us, the process should also be seamless and efficient,” she said. “Appointments should be scheduled quickly and follow-up and notes from the first consultation should be relayed back to the referring physician.” Mougalian added that special attention should also be paid to internal staffing challenges with even distribution of patient cases among appropriate specialists within the disease state. “Each team reviewed historical data to estimate the volume of new patient slots [and] made the appropriate adjustments in scheduling,” she said.

In contrast with their internal goal, investigators also strived to meet patient where they were. “The patient was at the center of this initiative and the No. 1 goal was to honor the patient’s choice, offering an appointment as soon as the patient wants it, and where the patient prefers,” Mougalian said. In tandem with this, she noted that managing patient expectations was also a critical component of the process, including the limitations that come with a next day appointment and other options that were available to them. An example roadmap for implementation is outlined in FIGURE 2.

In an analysis of patients with a data cutoff of February 2021, reasons why patients did not accept a next day appointment included the availability of a specific provider (49%) or a specific date was requested (27%). These rates dropped in an analysis between August 2021 and January 2022 to 38% and 20%, respectively.

Overall patients were satisfied with their scheduling through the next day access program with 92% of respondents (n = 864) stating that they were satisfied with their appointment choices. Further, 67% said the appointments exceeded their expectations with 29% stating that the appointment met their expectations. “We also asked on a scale of 1 to 10: How would you rate your first visit? The average was 9.4, and the median was 10 [ range, 4-10],” Mougalian said.

Oncologist feedback was also collected during the process with some providers noting that the appointments often felt inefficient and harder to navigate, especially if they did not have a comprehensive snapshot of the patient’s records for clinical review. “In general, the feedback was positive, and it was [noted] that patient satisfaction [as well as] excellent responses from providers who referred [patients] was a market differentiator and was going to drive referrals going forward,” Mougalian said.

PATIENT-FIRST FOCUS

At Moffitt Cancer Center, a similar program First Connect was initiated to establish care expectations for patients, enhance multidimensional approaches to care including access to clinical trials and personalized medicine, and improve access to visits with a 1-day turnaround from intake to appointment with a clinical subject matter expert. “The goal of First Connect was to not only create and provide patients with access, but [execute] it in a very meaningful way,” Pratt said.

The First Connect program starts with a call during which 3 main components are tackled: clinical assessment to support additional work-up requests and initiate a suspected clinical pathway; accelerate access to care by aligning the right provider with the right patient; and to build a foundational component with the patient. A

FIGURE 1. The Ideal State of Patient-Centric Access to Care

- **PATIENT**
  - Ease of self-referral
  - Efficient scheduling process
  - Timely pre-visit contact
  - Clear disease-specific expertise
  - Post consult follow-up call to confirm understanding/answer questions
  - Prompt treatment initiation; navigation and seamless transitions

- **REFERRING PHYSICIAN**
  - Referring physician familiarity with care team
  - Seamless, efficient referral process
  - E-consultation for select diagnosis
  - Availability of accepting physician for direct communication if desired
  - Standardized follow-up communication

- **INTAKE FACILITY**
  - Accurate new patient referral distribution based on disease specialty (decision algorithm)
  - Required patient data available for meaningful initial consultation
  - Team approach to ensure patient understanding and follow-up
  - Track and review patient satisfaction with interactions, process and care delivered
key differentiator of the construct of the Moffitt Cancer Center program is an increased focus on the emotional bond with the patient to help alleviate anxiety and build connections with the clinical team, Pratt said.

“The First Connect call is scheduled 24 hours after a patient has entered into our system,” Pratt said. “These calls are prior to a destination visit and serve as the connection that that patient can make with the clinic [and with] a provider who has the knowledge base about the disease can help set expectations. The most important piece is that the patient feels comfortable, understands, and is prepared for the destination visit.”

In addition to establishing that connection, Pratt noted that these calls are aimed at patient retention. “Approximately 12% of patients who call into our system, get put into a queue to be scheduled, and then we lose them, they never complete a new patient appointment,” Pratt said. “And that could be because they cancelled the appointment or because we were unable to ever get a hold of them, or that they [were a no show]. We really wanted this to be a way to make that connection and let the patient know, we care, we want to begin the process, and start collecting records to show you that we’re invested in your care and getting you to that consolation visit to start the journey.”

An important component of the pilot program is also generating an increased awareness of the institution’s offerings. “We want to make sure that we market to providers, so that if you’re [a clinician] who’s messaging to your patients is that their cancer diagnosis is your top priority, we now offer the opportunity to speak to a cancer expert within 1 day,” Timothy A. Price, MBA, FACHE, director of patient access at Moffitt Cancer Center said.

OVERCOMING BARRIERS TO IMPLEMENTATION AND CARE
Operational and cultural barriers present hurdles for both referring physicians and institutional teams to overcome. Multilevel problems are affecting diversity in clinical trial enrollment from a patient, health system, provider, and community aspect. Should the pilot programs reach the community in their intended ways, increased engagement between providers and referring clinicians may open the door for improved institutional infrastructure across sites to promote enrollment and recruitment. Although the changes may be minimal at this level, these programs afford the treating institutions data sets they did not previously have access to.

“These [programs are] important for the organization because they become a very rich data set,” Price said. “Really understanding patient preference and what’s actually happening with our scheduling data, [we can] harness the power [and] leverage that information for modality planning and looking at our clinical pathways for developing better clinical trial matching.”

Both Price and Mougalian drew attention to turnover and staffing issues which may affect the consistency of these programs to meet their objectives. “We saw that the number of available slots declined over time to and that we largely attribute to faculty departures,” Mougalian said.

“For us, from a [registered nurse] RN perspective, across the nation we have nursing challenges,” Price said. “They have clinical responsibilities [so we must] monitor to see if it is still appropriate delegation of responsibilities knowing some of the constraints that the departments. We wanted to call this out because post pandemic we have seen a rise in calls. How do we deal with those volumes?” One avenue Price noted is maintaining the high-quality call and providing training to get the most out of the interaction and establish that meaningful connection.

“We really need to be thinking about the capacity and the scalability of this,” Price said. “We need to take a look at how they manage their clinical duties and making sure that they’re getting credit for the work that they’re doing.”

Mougalian agreed noting that the minimum data that a patient and the referred physician receive prior to the first appointment should be meaningful. “The team should work together to ensure that the patient understands the plan of care that follow-up is established and that the patient is satisfied with the interactions, the process, and the care that’s delivered,” she said.

“There is no silver bullet for access,” Price said. “We really need to be doing things that have an upstream effect and [can change] the system.”

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Biomarkers Demonstrate Essential Role in Treatment Decisions in mCRC

by CHRIS RYAN

THE IDENTIFICATION OF KEY genetic markers has become integral in guiding the development of new treatments for patients with metastatic colorectal cancer (mCRC). The result is an expanded treatment armamentarium, which underscores the importance of genetic testing in this population, according to Christopher Lieu, MD.

Fifteen agents are approved by the FDA for the treatment of mCRC, including 10 biologic or targeted agents designed to treat patients with specific genetic alterations.1

“When you have a newly diagnosed patient with mCRC, the genomic information is not only important up front, but it’s certainly important down the line,” Lieu said. “Even now, we are still looking at [genetic testing] percentages at 60% to 70%, so it is still not being done early and often enough.”

In a presentation during the 7th Annual School of Gastrointestinal Oncology® (SOGO®), hosted by Physicians’ Education Resource® LLC (PER®), Lieu, associate director for clinical research and codirector of gastrointestinal medical oncology at the University of Colorado Cancer Center in Aurora, highlighted optimal treatment options for patients with BRAF V600E mutations, HER2 overexpression, and various biomarkers in mCRC, plus the effects of emerging agents in this space.

COMBINATIONS EMERGE IN BRAF V600E–MUTANT MCRC

Multiple clinical trials have pointed to the combination of encorafenib (Braftovi) and cetuximab (Erbitux) as the standard of care in the second line and later in patients with mCRC harboring BRAF V600E mutations, Lieu said.

In the phase 3 BEACON CRC trial (NCT02928224), 615 patients with BRAF V600E–mutated mCRC with disease progression after 1 or 2 prior regimens were randomized 1:1:1 to encorafenib and cetuximab; encorafenib, binimetinib (Mektovi), and cetuximab; investigator’s choice in the control arm of FOLFIRI (leucovorin calcium, fluorouracil, and irinotecan hydrochloride) or irinotecan plus cetuximab.2 The primary end points of overall survival (OS) and overall response rate (ORR) focused on the triplet vs the control regimen.

At a median follow-up of 12.8 months, the triplet produced a median OS of 9.3 months (95% CI, 8.1-10.8) compared with 5.9 months (95% CI, 5.1-7.1) in the control arm. However, the addition of binimetinib did not increase the OS benefit compared with the doublet therapy, which also achieved a median OS of 9.3 months (95% CI, 8.0-11.3).

Notably, instances of grade 3 or greater diarrhea were higher in the triplet arm and control arm (11% and 10%, respectively) vs the doublet arm (3%). “The doublet therapy, while there are [adverse] effects to it, was fairly well tolerated,” Lieu said.

A phase 1/2 trial (NCT04017650) is also exploring a triplet with an encorafenib and cetuximab backbone. In this study, nivolumab (Opdivo) is being added to the combination in patients with microsatellite-stable, BRAF V600E-mutated mCRC who had 1 or 2 prior lines of systemic therapy.3 Among the 22 evaluable patients in the phase 1 portion, the ORR was 50% (95% CI, 28%-72%) and the disease control rate (DCR) was 96% (95% CI, 77%-100%). Investigators plan to initiate phase 2 in 2022 and will explore encorafenib and cetuximab with or without nivolumab.

“There is some preclinical evidence suggesting that there is some T-cell infiltration with this regimen,” Lieu said. “You may be able to activate it with nivolumab. This trial is coming down the pipeline.”

The phase 2 ANCHOR-CRC trial (NCT03693170) also evaluated the encorafenib, binimetinib, and cetuximab triplet, except it was used in the first-line setting in the 90 patients with untreated, BRAF V600E-mutated mCRC.4 The triplet met its primary end point with a confirmed ORR of 47.8% (95% CI, 37.3%-58.3%) and a DCR of 88%. However, the median progression-free survival (PFS) was 5.8 months (95% CI, 4.6-6.4), and Lieu explained that the result fell short of what clinicians would
like to see in this setting (Table 2-12). "We would want to see a PFS that is higher than this," Lieu said. "Having said that, [this is] a bad, aggressive disease biology, so 6 months is still comparable to what we might expect.”

**ADDRESSING HER2 OVEREXPRESSION**

Overexpression of HER2 in patients with mCRC has become a meaningful marker for deciding therapy, Lieu explained. "When you get [a patient’s] targeted sequencing back and you see wild-type KRAS, NRAS, or BRAF, those are the patients you should be looking for HER2 amplification in," Lieu said.

HER2 amplification is enriched in KRAS wild-type disease, disrupting the benefit of anti-EGFR therapies for these patients. Consequently, patients with mCRC and HER2 amplification have demonstrated a shorter median PFS on anti-EGFR therapy of 2.9 months compared with 8.1 months for those with nonamplified disease (P < .001).14

Lieu noted that HER2 amplification should not be a hard stop for the use of anti-EGFR therapy, although he said it should give physicians pause—"particularly in patients who received prior anti-HER2 therapy," Lieu added.

Anti-HER2 inhibition was explored in the phase 2 HERACLES trial (NCT03225937) and phase 2 My Pathway trial (NCT02091141). In HERACLES, trastuzumab (Herceptin) and lapatinib (Tykerb) were combined in a single-arm study, generating an ORR of 30% (95% CI, 14%-50%) and a median time to progression of 21 weeks (95% CI, 16-32) in the 27 evaluable patients with HER2-amplified mCRC. The My Pathway trial elicited an ORR of 38% (24%-55%) and a median time to progression of 4.6 months (n = 62).6

Trastuzumab was also explored in combination with tucatinib (Tukysa) in the phase 2 MOUNTAINEER trial (NCT03043313), in which early data produced an ORR of 55%, a median PFS of 6.2 months, and a median OS of 17.3 months (n = 22).7 Final data on MOUNTAINEER are expected to read out later this year, Lieu said.

The novel antibody-drug conjugate fam-trastuzumab deruxtecan-nxki (Enhertu) is also being explored in this space. The agent could provide benefit for patients with HER2-overexpression and the early initiation of steroids are critical," Lieu said. "Keep in mind, there were 3 stage-5 events [in this study]. This is recoverable, but

**TABLE. Efficacy Outcomes Across Subsets in mCRC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>ORR (95% CI)</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
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<tbody>
<tr>
<td>BEACON CRC trial</td>
<td>Encorafenib and cetuximab (n = 205)</td>
<td>50% (28%-72%)</td>
<td>16.5 (5.4-38.1)</td>
<td>10.6 (6.1-26.3)</td>
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<tr>
<td></td>
<td>Encorafenib, binimetinib, and cetuximab (n = 205)</td>
<td>50% (28%-72%)</td>
<td>16.5 (5.4-38.1)</td>
<td>10.6 (6.1-26.3)</td>
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<tr>
<td></td>
<td>FOLFIRI or irinotecan plus cetuximab (n = 205)</td>
<td>50% (28%-72%)</td>
<td>16.5 (5.4-38.1)</td>
<td>10.6 (6.1-26.3)</td>
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<tr>
<td>NCT02928224</td>
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<tr>
<td>NCT03785249</td>
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<tr>
<td>KRYSTAL-1 trial</td>
<td>Adagrasib (n = 45)</td>
<td>22%</td>
<td>9.3 (95% CI, 8.0-11.3)</td>
<td>9.3 (8.1-10.8)</td>
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<tr>
<td>(NCT03785249)</td>
<td>Adagrasib and cetuximab (n = 28)</td>
<td>43%</td>
<td>9.3 (95% CI, 8.0-11.3)</td>
<td>9.3 (8.1-10.8)</td>
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<tr>
<td>MOUNTAINEER trial</td>
<td>Trastuzumab and lapatinib (n = 27)</td>
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<td>(NCT03225937)</td>
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<tr>
<td>ANCHOR-CRC trial</td>
<td>Trastuzumab and lapatinib (n = 62)</td>
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<td>(NCT02091141)</td>
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<td>DESTINY-CRC01 trial</td>
<td>Trastuzumab deruxtecan (n = 53)</td>
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<td>ORR (95% CI)</td>
<td>55%</td>
<td>38% (24%-55%)</td>
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<tr>
<td>Median PFS, weeks (95% CI)</td>
<td>21 (16-32)</td>
<td>21 (16-32)</td>
<td>21 (16-32)</td>
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<td>Median OS, months</td>
<td>17.3</td>
<td>17.3</td>
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<tr>
<td>MOUNTAINEER trial</td>
<td>Trastuzumab and tucatinib (n = 62)*</td>
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<td>(NCT03043313)</td>
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<tr>
<td>ORR</td>
<td>55%</td>
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<td>Median PFS, months</td>
<td>6.2</td>
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<tr>
<td>Median OS, months</td>
<td>17.3</td>
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<tr>
<td>CodeBreak 100 trial</td>
<td>Sotorasib (n = 62)</td>
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<td>(NCT03600883)</td>
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<td>Median PFS, months</td>
<td>4.0</td>
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<tr>
<td>Median OS, months</td>
<td>10.6</td>
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<tr>
<td>KRYS TAL-1 trial</td>
<td>Adagrasib (n = 45)</td>
<td>22%</td>
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<td>KEYNOTE-177 trial</td>
<td>Pembrolizumab (n = 153)</td>
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<td>(NCT02563002)</td>
<td>Investigator’s choice chemotherapy (n = 154)</td>
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<tr>
<td>Median PFS, months (95% CI)</td>
<td>16.5 (5.4-38.1)</td>
<td>8.2 (6.1-10.2)</td>
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<tr>
<td>Median PFS2, months (95% CI)</td>
<td>54.0 (44.4-NR)</td>
<td>24.9 (16.6-32.6)</td>
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<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (49.2-NR)</td>
<td>36.7 (27.6-NR)</td>
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<tr>
<td>CheckMate142 trial</td>
<td>Nivolumab and ipilimumab (n = 45)</td>
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<tr>
<td>(NCT02090188)</td>
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<tr>
<td>ORR</td>
<td>69%</td>
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<tr>
<td>24-month PFS</td>
<td>74%</td>
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<tr>
<td>24-month OS</td>
<td>79%</td>
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*First-line setting.

*Early data.

**DCR**, disease control rate; FOLFIRI, fluorouracil, leucovorin calcium, and irinotecan hydrochloride; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, second PFS; SD, stable disease; TTP, time to progression.
[physicians] must keep an eye out for interstitial lung disease.”

Lieu concluded that anti-HER2 combination therapy is the ideal treatment after first-line progression for patients with HER2-amplified mCRC, although trastuzumab deruxtecan can be an option for patients who have already received anti-HER2 therapies.

**PROGRESS IN KRAS G12C-MUTANT mCRC**

Patients with mCRC harboring KRAS G12C mutations have historically been difficult to treat, with this subset of disease considered “undruggable,” according to Lieu. However, recent clinical trials have started to move the needle forward in this space.

For example, sotorasib (Lumakras) elicited a 9.7% ORR, a median PFS of 4.0 months, and a median OS of 10.6 months in the 62 evaluable patients with KRAS G12C-mutated solid tumors in the phase 1/2 CodeBreak100 trial (NCT03600883).

Additionally, adagrasib generated a 22% ORR, a 64% stable disease (SD) rate, and an 87% DCR in the phase 1 KRYS-TAL-1 trial (NCT03785249; n = 45). Furthermore, KRYS-TAL-1 explored the combination of adagrasib and cetuximab, which elicited an ORR of 43%, an SD rate of 57%, and a DCR of 100% (n = 28) (Table 1–11).

“My hope is that when you see [patients with mCRC harboring KRAS G12C mutations] that you’ll strongly consider getting these patients to clinical trials,” Lieu said. “There should be some amount of benefit with [KRAS G12C inhibitors], particularly in our pretreated patients.”

**A CLEAR PATH IN MSI-H mCRC**

Immunotherapies utilizing pembrolizumab (Keytruda) or the combination of nivolumab and ipilimumab (Yervoy) have carved out a role in the use of panitumumab (Vectibix; n = 27). However, Lieu noted that those responses were not durable, and that more studies need to be conducted regarding this approach.

**REFERENCES**


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• Analyze testing strategies that may inform clinical decision making in the management of hematologic malignancies
• Apply clinical trial results to multiple lines of care in the management of hematologic malignancies
• Implement optimal strategies to treat hematologic malignancies
• Assess disparities in care for patients with hematologic malignancies
• Develop strategies to proactively prevent, minimize, and manage treatment-related toxicities in patients with leukemia, lymphoma, or multiple myeloma
• Discuss key emerging data sets regarding the management of patients with hematologic malignancies

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**SELECTING THE OPTIMAL FRONTLINE**

Treatment regimen for patients with unresectable metastatic colorectal cancer (mCRC) requires careful consideration of multiple characteristics, according to a presentation by Kristen K. Ciombor, MD, MSCI, at the 7th Annual School of Gastrointestinal Oncology (SOGO®), hosted by Physicians’ Education Resource®, LLC (PER®).

“We have a lot of [treatment] options nowadays, which is great, but sometimes it can be overwhelming,” said Ciombor, an associate professor of medicine in the Division of Hematology/Oncology within the Department of Medicine at Vanderbilt University Medical Center in Nashville, Tennessee. “It is not just biology [that we are considering] anymore. We have learned a lot about colorectal cancer and the different factors that will predict how well each of these options will work. But we [must] keep the patient in mind—performance status, comorbidities, their own goals and preferences, as well as the [effect] the treatment has on them.”

Ciombor began her presentation by outlining some of the primary decision drivers when choosing a first-line therapy for patients with mCRC. Driving factors consisted of tumor characteristics (ie, clinical presentation and RAS or BRAF mutation status), patient characteristics (ie, age and organ function), and treatment characteristics (ie, toxicity and quality of life). Ciombor noted that, often, patient and treatment characteristics become even more important when choosing later lines of therapy.

**INTENSIVE CHEMOTHERAPY REMAINS THE PRIMARY OPTION**

In a review of past clinical trials, Ciombor highlighted those evaluating the intensive chemotherapy regimens of FOLFOXIRI (5-fluorouracil, folinic acid, oxaliplatin, and irinotecan) and FOLFIRI (5-fluorouracil, folinic acid, and irinotecan) in patients with mCRC.

Specifically, she noted the phase 3 GONO trial (NCT01219920) and a phase 3 trial from the Hellenic Oncology Research Group, which evaluated FOLFOXIRI vs FOLFIRI; and also, the phase 3 TRIBE (NCT02339116) and phase 2 OLIVIA (NCT00778102) trials, which added bevacizumab (Avastin) to intensive chemotherapy.

As expected, response rates across these trials tended to increase with the addition of more chemotherapy, although this was often accompanied by an increase in toxicity. Overall, median overall survival (OS) and median progression-free survival (PFS) often favored the triplet regimens, which Ciombor identified as an important consideration when selecting a treatment regimen.

Building on the PFS findings from TRIBE, the phase 3 TRIBE2 study (NCT02339116) had FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen at disease progression (arm A; n = 340) compared with FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab at disease progression (arm B; n = 339). Patients received intensive treatment for up to 8 cycles and were deescalated to maintenance therapy. The primary end point was second PFS (PFS2). Patients in arm B experienced a median PFS2 of 19.2 months (95% CI, 15.1-17.5) in arm A (HR, 0.74; 95% CI, 0.63-0.88; P < .001). The median OS was 27.4 months (95% CI, 23.7-30.0) in arm B vs 22.5 months (95% CI, 20.7-24.8) in arm A (HR, 0.82; 95% CI, 0.68-0.98; P = .032).

“Building on the PFS findings from TRIBE, the phase 3 TRIBE2 study (NCT02339116) had FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen at disease progression (arm A; n = 340) compared with FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab at disease progression (arm B; n = 339). Patients received intensive treatment for up to 8 cycles and were deescalated to maintenance therapy. The primary end point was second PFS (PFS2). Patients in arm B experienced a median PFS2 of 19.2 months (95% CI, 15.1-17.5) in arm A (HR, 0.74; 95% CI, 0.63-0.88; P < .001). The median OS was 27.4 months (95% CI, 23.7-30.0) in arm B vs 22.5 months (95% CI, 20.7-24.8) in arm A (HR, 0.82; 95% CI, 0.68-0.98; P = .032).”

**TABLE. Outcomes of Doublet Regimens in mCRC**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fluoropyrimidine plus bevacizumab (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>10.0 (9.0-11.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>19.7 (15.5-25.5)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>44.7% (82.76%-89.5%)</td>
</tr>
</tbody>
</table>

**BIOLOGICS AND TUMOR SIDEDNESS**

Ciombor moved into a discussion of the different biologic and doublet combinations available for mCRC, noting that because of the varying overall response rates (ORRs), PFS, and OS rate, clinicians should consider patient-specific factors when deciding. Using tumor sidedness as an example, Ciombor focused on an analysis of the phase 3 CALGB/SWOG 80405 trial (NCT00265850), in which investigators compared the addition of cetuximab (Erbitux) with the addition of bevacizumab with first-line doublet chemotherapy and found no difference in terms of OS or PFS.

However, a subgroup analysis showed that primary tumor sidedness appeared to influence OS. Patients with left-sided tumors had a superior median OS in both the bevacizumab and cetuximab groups, 31.4 months (95% CI, 28.3-33.6) and 36.0 months (95% CI, 32.6-40.3), respectively. Among patients with right-sided tumors...
In a review of data from triplet vs doublet chemotherapy regimens, Ciombor said doublet regimens often displayed better response rates vs single-agent regimens, but OS was not necessarily always superior in the doublet regimens.

"That’s an important point that factors in patient tumor burden and their goal [of treatment]," Ciombor said. "At the end of the day, OS is clearly a better long-term end point, but response rate can have its role, too, depending on the patient."

In the Japanese RESPECT trial (UMIN000008866), the addition of oxaliplatin to fluoropyrimidine plus bevacizumab was evaluated in elderly patients with mCRC. Patients were randomized to receive oxaliplatin plus fluoropyrimidine plus bevacizumab (n = 126) or fluoropyrimidine plus bevacizumab (n = 125). To be eligible for the trial, patients needed to be between ages of 70 to 74 years with an ECOG performance score of 2, or at least aged 75 years with an ECOG performance score of 0 to 2.6

Results from the trial showed that patients treated with the oxaliplatin combination experienced a median PFS of 10.0 months (95% CI, 9.0-11.2) compared with 9.4 months (95% CI, 8.3-10.3) among those who did not (HR, 0.837; 95% CI, 0.648-1.033; P = .086). The median OS was 19.7 months (95% CI, 15.5-25.5) and 21.3 months (95% CI, 18.7-24.3), respectively (HR, 1.054; 0.810-1.372). However, a difference in ORR was observed: Patients who had oxaliplatin added to their treatment regimen had an ORR of 47.7% compared with 29.5% in those who did not.

"Look for the patients who need a response—that may be the portion of patients who would benefit more from doublet therapy," Ciombor said. "But other [patients who are] 70 [years or older] can avoid the toxicities of oxaliplatin. This is definitely a discussion to be had with your patients based on their goals and preferences."

In the phase 2 TASCO1 trial (NCT02743221), trifluridine/tipiracil plus bevacizumab (TT-B) was compared to capecitabine plus bevacizumab (C-B) as first-line therapy for patients with mCRC who are not candidates for intensive therapy. Patients were randomized 1:1 and were stratified by RAS status, ECOG performance score, and region. The median age of patients in the TT-B group (n = 77) was 73 years of age (range, 43-83) and 75.5 years of age (range, 33-91) in the C-B arm (n = 76).7

Data from the trial showed that the median PFS for patients in the TT-B cohort was 9.23 months (95% CI, 7.59-11.56) vs 7.82 months (95% CI, 5.55-10.15) in the C-B group (HR, 0.71; 0.48-1.06). The median OS was 22.31 months (95% CI, 18.00-23.69) and 17.67 months (95% CI, 12.58-19.81), respectively (HR, 0.78; 0.32-0.98).

Considering the findings from TASCO1, the phase 3 SOLSTICE study (NCT03869892) was initiated to compare TT-B with C-B in patients with treatment-naïve mCRC who are not eligible for standard doublet chemotherapy regimens. Patients were randomized to the TT-B group (n = 426) or the C-B group (n = 430) and were stratified based on ECOG performance status, tumor localization, and the reason for not being eligible for intensive therapy. The primary end point was PFS.8

Results showed that T-B was not superior to C-B for PFS; specifically, the median PFS was 9.4 months (95% CI, 9.1-10.9) compared with 9.3 months (95% CI, 8.9-9.9), respectively (HR, 0.87; 0.75-1.02; P = .0464). Ciombor noted that the disease control rate (DCR) for both regimens was relatively high, at 86.4% (95% CI, 82.76%-89.5%) and 85.1% (95% CI, 81.40%-88.40%), respectively (TABLE 4*). "The DCR was quite high in these patients [and] that’s something we always think about and worry about…. We want to control their disease above anything, [and these data showed] a very high proportion [of patients] who had disease control despite having less intensive therapy," Ciombor said.

REFERENCES

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

- **1-year DFS rate**: 97%
- **2-year DFS rate**: 90%
- **3-year DFS rate**: 78%

**Consistent results with or without prior adjuvant chemotherapy**\(^2\)\(^\dagger\)

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

---

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

\(\dagger\) Control arm = placebo.

Combination chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).\(^1\)

\(\dagger\) Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.16 (95% CI: 0.10, 0.26) and for patients without adjuvant chemotherapy was HR=0.22 (95% CI: 0.15, 0.40).\(^2\)

DFS, disease-free survival; EGFRm, epidermal growth factor receptor mutation positive; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; QoL, quality of life; TKI, tyrosine kinase inhibitor.

**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

TAGRISSO is a registered trademark of the AstraZeneca group of companies.©2021 AstraZeneca. All rights reserved. US-53566 5/21
‡ 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.1

† Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases

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 who continue long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.

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

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

- 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 by an FDA-approved test prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise males with female partners 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.

TAGRISSO® (osimertinib) tablets, for oral use
Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
Active Treatment of ESRF Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)
TAGRISSO is indicated as an active therapy for 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 (2.2) in the full Prescribing Information].

Previously Treated ESRF TKI-Mutation-Positive Metastatic NSCLC
TAGRISSO is indicated for the treatment of adult patients with metastatic ESRF TKI-mutation-positive NSCLC whose tumors have EGFR TKI resistance mutations, as determined by an FDA-approved test. Disease progression on or after EGFR TKI systemic therapy is required for patients with whom EGFR TKI systemic therapy cannot be administered.

Select patients for the first-line treatment of metastatic ESRF mutation-positive NSCLC based on the results of EGFR mutation status testing [see Warnings and Precautions (5.4) in the full Prescribing Information].

If these mutations are not detected in a plasma specimen, tissue tumor must be used.

DOSAGE AND ADMINISTRATION
Patient Selection
Select patients with resectable tumors for the first-line treatment of metastatic ESRF TKI-mutation-positive NSCLC with TAGRISSO based on the results of EGFR mutation status testing [see Warnings and Precautions (5.4) in the full Prescribing Information].

Recommended Dosage Regimen
The recommended dosage of TAGRISSO is 80 mg tablet once a day. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Contraindications
Active treatment of patients with lung cancer who have experienced interstitial lung disease is not recommended.

Dose Modification
TAGRISSO should be discontinued for serious adverse reactions, those leading to hospitalization, or those that lead to a dose reduction.

Adverse Reactions

Table 1. Recommended Dosage Modification for TAGRISSO

Target Organ | Adverse Reaction | Revised Dose* |
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Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=267)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea 20%</td>
<td>22%</td>
<td>72%</td>
<td>57%</td>
</tr>
<tr>
<td>Stomatitis 22%</td>
<td>23%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea 14%</td>
<td>14%</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Constipation 15%</td>
<td>10%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting 11%</td>
<td>11%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash 59%</td>
<td>59%</td>
<td>50%</td>
<td>57%</td>
</tr>
<tr>
<td>Dry skin 3%</td>
<td>3%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Nail toxicity‡ 3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus‡ 17%</td>
<td>17%</td>
<td>4%</td>
<td>17%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue‡ 21%</td>
<td>14%</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td>Pyrexia 10%</td>
<td>10%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite 12%</td>
<td>10%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection 10%</td>
<td>10%</td>
<td>7%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Clinically relevant adverse reactions in FLAURA in ≥10% of patients receiving TAGRISSO were alopecia (7%), epistaxis (6%), interstitial lung disease (3%), urticaria (2.2%), palmar-plantar erythrodysesthesia syndrome (1.4%), QTc interval prolongation (1.1%), and leukopenia (2.4%). QTc interval prolongation represents the incidence of patients who had a QTcF interval ≥500msec.

Table 5. Laboratory Abnormalities Worsening from Baseline in ≥2% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=267)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia 63%</td>
<td>68%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>Anemia 5%</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukopenia 5%</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Thrombocytopenia 56%</td>
<td>57%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Neutropenia 41%</td>
<td>43%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia‡ 37%</td>
<td>37%</td>
<td>31%</td>
<td>35%</td>
</tr>
<tr>
<td>Hematocrit/hemoglobin 30%</td>
<td>30%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Creatinine 26%</td>
<td>27%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Glucose 22%</td>
<td>23%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Increased AL 21%</td>
<td>21%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Hyperbilirubinemia 16%</td>
<td>16%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*([see Nonclinical Toxicology (13.1) in the full Prescribing Information]).† Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and on-study laboratory measurements available.‡ Includes nail bed disorder, nail bed inflammation, nail bed infection, nail pigmentation, skin disorder, nail toxicity, nail dystrophy, nail infection, nail rigidity, onychogryphosis, onychomadesis,onychophagy,onycholysis,polydactyly,radiculopathy,atrophy,brachydactyly,digital clubbing,digital deformity,digitalis,digitalis intoxication,digital necrosis, epidermolysis bullosa, epidermolysis bullosa acquisita, epidermolysis bullosa dystrophica, epidermolysis bullosa simplex, epidermolysis bullosa neonatorum, epidermolysis bullosa punctata, epidermolysis bullosa tarda, epidermolysis bullosa verruciformis, keratitis (1.1%), and erythema multiform (0.7%). QTc interval prolongation represents the incidence of patients who had a QTcF interval ≥500msec.

Table 6. Laboratory Abnormalities Worsening from Baseline in ≥2% of Patients in AURA3

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
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<tr>
<td>Lymphopenia 64%</td>
<td>66%</td>
<td>11%</td>
<td>11%</td>
<td>.0005</td>
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<tr>
<td>Anemia 16%</td>
<td>16%</td>
<td>1%</td>
<td>1%</td>
<td>&lt;.0001</td>
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<tr>
<td>Leukopenia 14%</td>
<td>15%</td>
<td>0%</td>
<td>1%</td>
<td>.0005</td>
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<tr>
<td>Thrombocytopenia 11%</td>
<td>11%</td>
<td>0%</td>
<td>0%</td>
<td>.0005</td>
</tr>
<tr>
<td>Neutropenia 1%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>.0005</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hyperglycemia‡ 32%</td>
<td>32%</td>
<td>1%</td>
<td>1%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hematocrit/hemoglobin 30%</td>
<td>30%</td>
<td>0%</td>
<td>11%</td>
<td>.0005</td>
</tr>
<tr>
<td>Creatinine 26%</td>
<td>27%</td>
<td>1%</td>
<td>1%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Glucose 22%</td>
<td>23%</td>
<td>43%</td>
<td>43%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Increased AL 21%</td>
<td>21%</td>
<td>7%</td>
<td>7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hyperbilirubinemia 16%</td>
<td>16%</td>
<td>4%</td>
<td>4%</td>
<td>.0005</td>
</tr>
</tbody>
</table>

*([see Nonclinical Toxicology (13.1) in the full Prescribing Information]).† Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and on-study laboratory measurements available.‡ Includes nail bed disorder, nail bed inflammation, nail bed infection, nail pigmentation, skin disorder, nail toxicity, nail dystrophy, nail infection, nail rigidity, onychogryphosis, onychomadesis,onychophagy,onycholysis,polydactyly,radiculopathy,atrophy,brachydactyly,digital clubbing,digital deformity,digitalis,digitalis intoxication,digital necrosis, epidermolysis bullosa, epidermolysis bullosa acquisita, epidermolysis bullosa dystrophica, epidermolysis bullosa simplex, epidermolysis bullosa neonatorum, epidermolysis bullosa punctata, epidermolysis bullosa tarda, epidermolysis bullosa verruciformis, keratitis (1.1%), and erythema multiform (0.7%). QTc interval prolongation represents the incidence of patients who had a QTcF interval ≥500msec.

The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 449 patients with untreated or metastatic EGFR T790M mutation-positive NSCLC who had progressed disease following first line EGFR TKI treatment. A total of 279 patients received TAGRISSO 80 mg orally once daily until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment. A total of 136 patients received pemelrotin plus either carboplatin or cisplatin every three weeks for up to 6 cycles; patients without disease progression after 4 cycles of chemotherapy could continue maintenance treatment until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment. Left Ventricular Ejection Fraction (LVEF) was evaluated at screening and every 12 weeks. The median duration of treatment was 8.1 months for patients treated with TAGRISSO and 4.2 months for chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 years (68%), female (65%), Asian (86%), never smokers (86%), and ECOG PS 0 or 1 (100%).
PD-L1 Expression Guides Immunotherapy Decisions in Esophageal Adenocarcinoma

by JACKIE COLLINS

ALTHOUGH APPROVED IMMUNOTHERAPY treatment options for patients with esophageal adenocarcinoma (EAC) are not dependent on PD-L1 expression, it may serve as a prognostic marker for decision-making in the first line, according to a presentation by David H. Wang, MD, PhD, at the 7th Annual School of Gastrointestinal Oncology® (SOGO®).1

Wang, an associate professor in the Department of Internal Medicine at UT Southwestern Medical Center in Dallas, Texas, presented findings from subgroup analyses of patients 2 in pivotal studies, results of which led to the approval of pembrolizumab (Keytruda) and nivolumab (Opdivo), respectively.2,3

"There is a lot of new data that has been coming out recently and there are a lot of confusing questions in particular, what is the cut off biomarkers in patients’ tumors necessary to recommend certain therapies," Wang said.

PEMBROLIZUMAB

Wang presented data from the subgroup of patients with EAC treated in the phase 3 KEYNOTE-590 trial (NCT03189719). Results from the overall population led to the FDA approval of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic or locally advanced esophageal or gastroesophageal (GEJ) carcinoma who are not candidates for surgical resection or definitive chemoradiation.1

Wang noted that there was no statistically significant benefit observed in this subgroup overall. The median overall survival (OS) was 11.6 months for the 99 patients who received pembrolizumab plus chemotherapy vs 9.9 months for those who received chemotherapy alone (HR, 0.74; 95% CI, 0.54-1.02).4 Outcomes were stratified by PD-L1 combined positive score (CPS) of at least 10 and compared with those who had a PD-L1 CPS of less than 10. In the subgroup of 43 patients with EAC with a PD-L1 CPS of at least 10 who received pembrolizumab plus platinum and fluoropyrimidine-based chemotherapy, the median OS was 12.1 months (95% CI, 9.6-18.7) compared with 10.7 months (95% CI, 8.2-15.3) for 54 patients who received chemotherapy alone (HR, 0.83; 95% CI, 0.52-1.34). The median progression-free survival (PFS) was 8.0 months (95% CI, 6.0-8.3) vs 6.0 months (95% CI, 4.1-6.2), respectively (HR, 0.49; 95% CI, 0.30-0.81).5 As for those with EAC with a PD-L1 CPS of less than 10, the median OS for the 54 patients who received the combination was 12.7 months (95% CI, 8.1-16.1) vs 9.9 months (95% CI, 5.5-13.0) for the 46 patients who received chemotherapy alone (HR, 0.66; 95% CI, 0.42-1.04). The median PFS was 6.3 months (95% CI, 5.6-8.3) vs 5.7 months (95% CI, 3.3-6.3), respectively (HR, 0.76; 95% CI, 0.49-1.19) (TABLE 4,5).

"If you look at [patients with] EAC with a CPS of at least 10, there is no OS benefit but there is a PFS benefit," Wang explained. "There was no statistically significant benefit in patients with a CPS less than 10."

He noted that although there is no PD-L1 requirement in the FDA approval, “[patients] really should have a PD-L1 of at least 10 and that is what is recommended by the European Medicines Agency” for pembrolizumab in this patient population.

NIVOLUMAB

Wang overviewed similar subpopulations enrolled in the phase 3 CheckMate 649 trial (NCT02872116). Results of the trial led to the FDA approval of nivolumab in combination with fluoropyrimidine and platinum-containing chemotherapy or chemotherapy alone.6

<table>
<thead>
<tr>
<th>Expression cutoff</th>
<th>Median OS, months (95% CI)</th>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-590 trial (NCT03189719)</td>
<td>Pembrolizumab + chemotherapy (n = 641)</td>
<td>Chemotherapy alone (n = 655)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 10</td>
<td>12.1 (9.6-18.7)</td>
<td>10.7 (8.2-15.3)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.83; 95% CI, 0.52-1.34</td>
<td>8.0 (6.0-8.3)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab + chemotherapy (n = 54)</td>
<td>Chemotherapy alone (n = 46)</td>
</tr>
<tr>
<td>PD-L1 CPS &lt; 10</td>
<td>12.7 (8.1-16.1)</td>
<td>8.4 (5.5-13.0)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.66; 95% CI, 0.42-1.04</td>
<td>6.3 (5.6-8.3)</td>
</tr>
</tbody>
</table>

CheckMate 649 trial (NCT02872116)

<table>
<thead>
<tr>
<th>Expression cutoff</th>
<th>Median OS, months (95% CI)</th>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + chemotherapy (n = 641)</td>
<td>Chemotherapy alone (n = 655)</td>
<td></td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 5</td>
<td>14.4 (13.1-16.2; 473)</td>
<td>11.1 (10.0-12.1; 482)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.71; 95% CI, 0.59-0.86; P = .0001</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>Nivolumab + chemotherapy (n = 473)</td>
<td>Chemotherapy alone (n = 482)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 1</td>
<td>14.0 (12.6-15.0)</td>
<td>11.3 (10.6-12.3)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.77; 99.3% CI, 0.64-0.92; P = .0001</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Nivolumab + chemotherapy (n = 482)</td>
<td>Chemotherapy alone (n = 473)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 1</td>
<td>14.0 (12.6-15.0)</td>
<td>11.3 (10.6-12.3)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.77; 99.3% CI, 0.64-0.92; P = .0001</td>
<td>7.5</td>
</tr>
</tbody>
</table>

CPS, combined positive score; EAC, esophageal adenocarcinoma; OS, overall survival; PFS, progression-free survival.
chemotherapy for the treatment of patients with advanced or metastatic gastric cancer, GEJ cancer, and EAC.\(^1\) Wang focused on the notable comparison of outcomes in patients with EAC with a PD-L1 CPS of at least 5 vs a PD-L1 CPS of at least 1. He noted that this was the first trial to evaluate PD-L1 CPS using the cutoff of 5.

In the subgroup of 473 patients with EAC with a PD-L1 CPS of at least 5 who received nivolumab plus fluoropyrimidine and platinum-containing chemotherapy, the median OS was 14.4 months (95% CI, 13.1-16.2); this was 11.1 months (95% CI, 10.0-12.1) for the 482 patients in this population who received chemotherapy alone (HR, 0.71; 95% CI, 0.59-0.86; \(P = .0001\)). The median PFS was 7.7 months and 6.1 months, respectively (HR, 0.69; 95% CI, 0.59-0.80; \(P = .0073\)).

Additionally, for the 641 patients with a PD-L1 CPS of at least 1 in the investigational arm, the median OS was 14.0 months (95% CI, 12.6-15.0) and 11.3 months (95% CI, 10.6-12.3) for the 655 patients who received chemotherapy alone (HR, 0.77; 99.3% CI, 0.64-0.92; \(P = .0001\)). The median PFS was 7.5 months and 6.9 months, respectively (HR, 0.75; 95% CI, 0.65-0.85; \(P = .139\)) (TABLE\(^2\)).

“Patients with PD-L1 less than 1 do not benefit from getting adjuvant [nivolumab plus fluoropyrimidine and platinum-containing chemotherapy],” Wang said. “The population of patients with PD-L1 more than 1 benefit, [but] the question is whether [data are] pulled by patients that have PD-L1 more than 5. Given the survival curves and the number of [subgroups] of patients involved, [physicians] should have a conversation with patients. But I would typically recommend [immune checkpoint inhibition] for patients with PD-L1 of at least 1.”

REFERENCES

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**Marshall Highlights the Importance of Distinct Approaches to GI Cancers**

**by JACKIE COLLINS**

**DISTINCTIONS IN HISTOLOGY,** molecular profiles, and tumor location have set diverging treatment courses for patients with gastrointestinal (GI) cancers, according to John L. Marshall, MD. To address these varying care pathways, cross-functional approaches to education and care have become paramount for clinicians.

Marshall was the coleader of the 7th Annual School of Gastrointestinal Oncology\(^\text{®}\) (SOGO\(^\text{®}\)). “The main takeaway from this meeting is that there is a lot to learn,” said Marshall, chief of the Division of Hematology/Oncology at Medstar Georgetown University Hospital and director of The Ruesch Center for the Cure of Gastrointestinal Cancers in Washington, DC, in an interview with OncologyLive\(^\text{®}\). “We learned a lot, we have moved the bar, but we have a long way to go. We know there are common malignancies, we know there are highly fatal malignancies as a group, and we know a lot of [clinicians] are familiar with them. It used to be an easy disease or group of diseases to take care of, but there is a lot going on in GI cancers.”

Marshall provided an overview of the main highlights from the meeting, including progress made, anticipated trends in research, and optimal treatment benefits for GI cancer.

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**A** How has bile duct cancer set itself apart from other GI cancers?

When I first started in GI cancers, there was not much called “bile duct cancer.” We used to call that “unknown primaries in the liver” because you were not supposed to get adenocarcinomas in the liver. It has only been in the past 10 plus years that we have recognized that these adenocarcinomas in the liver cleanse [the body] of carcinomas and bile duct cancers.

We have to divide them into 3 categories [and] here I like to use a tree [analogy]: there is the trunk of the tree, and that is the common bile duct; there are the branches, and those are intrahepatic bile ducts; and then there is that kind of knot off the side of the tree, and that is the gallbladder. And as we think about those 3 parts of the tree—the 3 parts of the bile system—we are increasingly recognizing that they are different. Yes, they are all adenocarcinomas [and] they are mostly included in all the clinical trials. But when we look at molecular profiling or precision medicine, we are seeing that they have different characteristics.

So just like we did in upper GI cancers, where we separated esophageal, GI junction, and stomach cancers, we are now increasingly separating common bile duct intrahepatic and gallbladder from each other.

---

**A** How has bile duct cancer moved from obscurity to star of the show?

What has been going on in bile duct cancers? The answer is a lot. With [the advent of] precision medicine, we are learning that there are important molecular subtypes—\(FGFR\) fusions or alterations, \(IDH1\) alterations or mutations, and immunotherapy biomarkers—all of which are present in a high-enough percentage that they are worth looking for. There are therapies that have significant improvements in outcome when they are applied. Just as you would measure molecular tests for almost all your cancers, the same now is true for cholangiocarcinoma and bile duct cancers.

Now, one of the other places it has become the star of the show is that it is one more of our GI cancers where immunotherapy has worked, is in the TOPAZ-1 clinical trial [NCT03875235], a randomized study of gemcitabine plus cisplatin vs gemcitabine plus cisplatin and immunotherapy. What we saw was an improvement in overall survival in that patient population and we are expecting an FDA approval in that space. So immunotherapy [is making] its way to bile duct cancers as well.

[Bile duct cancer] is absolutely not that rare of a cancer if you know what you are looking for. Precision medicine is key, and immunotherapy is an important part of that.
What are the anticipated trends for research in this area that will have the greatest effect on the landscape?

When we look at next steps with cholangiocarcinoma and bowel cancers, first we are applying the precision medicine. And so we have subcategories of this based on not only anatomy, but now also molecular profile. With each of those areas, we are seeing further activity of combinations and different lines of therapy.

We are also increasingly seeing liver-directed therapy approaches [and we are doing] this with our interventional surgical and radiation [colleagues] who are helping us to manage this. We have a lot of patients with liver-dominant problems. That sort of multidimensional approach is required in optimal management.

And then, [we ask the question]: How do we make the toehold we have with immunotherapy get bigger through combinations and other molecular characterizations to better understand who should get in therapy and who should not? [There is] a lot of ongoing work in the biotech cancer space.

What were some of the key takeaways from the Medical Crossfire® debate on the incorporation of immunotherapy in GI cancers?

There is so much going on [in immunotherapy]. It is really the Wild West.

We were looking at immunotherapy being applied to GI cancers and so we walked through the GI tract [and asked]: Does PD-L1 expression matter in upper GI cancers? And we decided: yes, it does. Immunotherapy has a place through lines of therapy even in the adjuvant setting in certain cancers. PD-L1 expression probably is a good marker for who benefits and who does not.

We [also] looked at hepatocellular carcinoma [HCC], [a space that is] dominated by immunotherapy approaches, in the front line and other lines of therapy. Durvalumab [Imfinzi] showed positive results even as a single agent in HCC. The data with durvalumab in cholangiocarcinoma and bile duct cancers were there.

In pancreas cancer, [immunotherapy] is still dormant; we have not figured out how to crack that nut. But then if you go on further south to colorectal cancer, particularly rectal cancer, we talked about MSI-H [microsatellite instability-high] in the neoadjuvant setting [and asked]: do we use immuno-oncology [IO] therapy in the neoadjuvant setting and in rectal cancer?

There are some highly provocative small phase 2 experience data showing 11 out of 11 [patients] having a complete clinical and radiographic response with just IO therapy and MSI-H rectal cancer. That would be transformative.

What can or should be done to ensure patients receive the optimal benefit from these approaches?

One of the main themes of the meeting was that molecular profiling is critical. To identify those patients who are candidates for immunother-apy and precision medicine target therapy, you need adequate tissue, to understand what the tests measure, and then apply those in a multi-disciplinary fashion to optimize treatment for our patients.

We are increasingly emphasizing organ preservation. And so we are trying to not only care for our patients but also allow them to maintain their quality of life. What we are seeing is what we were hoping: that these precision medicine tools are giving us those opportunities to both improve outcomes and maintain quality of life.
Please see full Important Safety Information on the following pages.

**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.

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**TUKYSA trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine**

**Reduced risk of disease progression or death by 46%**

**Median PFS:** 7.8 months (95% CI: 7.5–9.6) vs 5.6 months (95% CI: 4.2–7.1); HR = 0.54 (95% CI: 0.42–0.71); *P* < 0.00001

**Extended median OS by 4.5 months**

**Median OS:** 21.9 months (95% CI: 18.3–31.0) vs 17.4 months (95% CI: 13.6–19.9); HR = 0.66 (95% CI: 0.50–0.87); *P* = 0.0048

The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.1

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**CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.**
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 rash

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 leading 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 leading 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.
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 5.8 months (95% CI: 4.2-7.1) in the control arm**

**EXPLORATORY ANALYSIS**

- **PFS at 12 months**
  - ~3x as many patients were progression-free
  
  - **TUKYSA ARM: 33% (33.1%; 95% CI: 26.6-39.7)**
  - **CONTROL ARM: 12% (12.3%; 95% CI: 6.0-20.9)**

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**Lab Abnormalities**

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

**Drug Interactions**

- **Strong CYP3A/Moderate CYP2C8 Inducers**: Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.

- **Strong or Moderate CYP2C8 Inhibitors**: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

- **CYP3A Substrates**: Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

- **P-gp Substrates**: Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**

- **Lactation**: Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.

- **Renal Impairment**: Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.

- **Hepatic Impairment**: Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References:


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Seagen

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TUKYSAhcp.com
TABLE 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

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.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors:

For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

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.

**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 antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

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

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

**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-planter erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
<th>Grade (%)</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>3</td>
<td>4</td>
<td>All</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
<td>0.5</td>
<td>53</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>3.7</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>3</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>32</td>
<td>2.5</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-planter erythrodysesthesia syndrome</td>
<td>63</td>
<td>13</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>Rash†</td>
<td>20</td>
<td>0.7</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
<td>0.5</td>
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<td>Nausea</td>
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<td>36</td>
<td>3</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>32</td>
<td>2.5</td>
<td>0</td>
<td>21</td>
</tr>
</tbody>
</table>

1. Graded 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
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.

**Drugs**

**Effects of Other Drugs on TUKYSA**

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

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

**Lactation**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

**Females and Males of Reproductive Potential**

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

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

**Geriatric Use:** In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in 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 (5%), vomiting (6%), and anemia (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:** 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.

**Drugs**

**Effects of Other Drugs on TUKYSA**

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

**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.
Novel FSHR-Mediated CER T Method Is Under Exploration in Recurrent Ovarian Cancer

by RYAN SCOTT

AN INVESTIGATIVE FOLLICLE-STIMULATING hormone receptor (FSHR)-mediated chimeric endocrine receptor (CER) T-cell technology is under exploration in patients with recurrent ovarian cancer as part of a phase 1 trial (NCT05316129). Several chimeric antigen receptor (CAR) T-cell therapies have proved to be efficacious in hematological cancers. However, developing a safe and effective CAR T-cell approach for solid tumors has remained a challenge.

For this reason, investigators have explored targets expressed on cancerous, but not healthy, tissue that may provide a pathway forward for patients who are resistant to or have no alternative treatment options. A novel autologous cell therapy, composed of engineered T cells that target FSHR, which is detected at immunological levels exclusively on the granulosa cells of the ovaries, will be explored under a collaboration between Anixa Biosciences, Inc and Moffitt Cancer Center in the phase 1 study.

“We don’t call them chimeric antigen receptors, because there is no antigen,” Jose Conejo-Garcia, MD, PhD, chair of the Department of Immunology and program coleader of immunology at Moffitt Cancer Center in Tampa, Florida, said in an interview with OncologyLive®. “The principle is the same; we are engineering the T cells of the patient to express our chimeric receptor that contains the same elements of a classical CAR—CD3ζ signaling domain, transmembrane domain, a hinge domain. But the target in motif, which is an antibody fragment [in a classical CAR], in our case is the FSH hormone [in our case].”

BUILDING A CASE FOR FSH

Conejo-Garcia noted that FSH is overexpressed in approximately 60% of patients with ovarian cancer, and preclinical research has demonstrated that FSHR becomes upregulated upon resistance to chemotherapy. In an analysis of 404 high-grade serous ovarian carcinomas, FSHR messenger RNA were detectable in 56.4% of samples. Additionally, investigators noted that FSHR was expressed in the RING1, TOV-21G, and OVTKO clear cell ovarian cell lines, representing an opportunity for patients who do not have effective therapeutic options.

“For every patient who expresses the receptor for the FSH hormone, the evidence we have is that before chemotherapy, before recurrence, patient’s express, the FSH receptor in approximately 60% of ovarian cancers of different histological types, some of [which] are very much unmet needs. For instance, clear cell ovarian cancer is devoid of effective treatment,” Conejo-Garcia said.

He added that there is also preliminary evidence that the FSHR is expressed in malignancies other than ovarian cancer. For instance, in an analysis of 1095 breast carcinomas in The Cancer Genome Atlas, 4.7% of samples were positive for FSHR expression. “We are understanding some biology, [and] we hope that this [approach can] be extended to other patients if it is successful and safe,” he said.

In targeting FSHR, investigators hypothesize that T cells expressing full-length FSHR-directed chimeric receptors would promote therapeutic effects against ovarian cancer cells.

Additionally, the restricted expression pattern of FSHR proposed an option for therapy that may circumvent off-target adverse effects, some of which may be fatal.

“All the evidence we have indicates [this CER T-cell therapy approach] behaves exactly as CAR T-cell therapy, with the only difference [being] that the targeted motif is different. We are selecting 4-1BB as the stimulatory domain,” Conejo-Garcia said. “Other CAR T-cell [therapies] use CD28 [as a stimulatory domain, which] can be more sensitive. However, what we have [learned] from patients who have received CAR T cells is that 4-1BB-based CAR [T-cell therapies] appear to be more persistent. We decided to go for persistence to prevent further recurrence, as opposed to enhancing cytotoxic activity in the short-term, which is what CD28-based [therapies] appear to provide.”

No safety signals were reported in mouse models at any level, and investigators reported no alternative targeting of healthy tissue in the study.

MOVING INTO PHASE 1

In April 2021, progress in bringing the CER T-cell therapy to trial was stalled when the FDA requested more information to support the investigational new drug application submitted for the individualized therapy. In August 2021, the clinical trial investigating CER-T in ovarian cancer was cleared for initiation, which officially began in March 2022.

The phase 1 trial is recruiting patients with a pathologically confirmed diagnosis of high-grade epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma that expresses the FSHR antigen. Further, cancers must be serous, endometrioid, clear cell, mucinous, mixed epithelial, or undifferentiated, and patients with pure sarcoma, stromal, or germ cell tumors are ineligible for enrollment.
Further enrollment criteria include an ECOG performance status of 2 or better, life expectancy of at least 3 months, and an acceptable bone marrow, renal, and hepatic function. Patients also must have received 1 prior platinum-based chemotherapy regimen, be considered refractory to treatment, and have measurable disease. “Patients who don’t respond to cisplatin and who have recurrent disease are, sadly, devoid of therapeutic options [in most cases],” Conejo-Garcia said.

Additionally, patients with a known germline or somatic BRCA pathogenic mutation are eligible for enrollment and should have previously received a PARP inhibitor and subsequently experienced disease progression. Patients can, but are not required to, receive 6 additional previous chemotherapy treatment regimens. The trial is also aiming to include a patient population that is devoid of available treatment options, according to Conejo-Garcia.

The estimated enrollment for the trial is 48 participants, who will intraperitoneally or intravenously receive 1 infusion of FSHR T cells at the following dose levels (DL): 1 × 10⁵ (DL1), 48 participants, who will intraperitoneally or intravenously receive 1 infusion of FSHR T cells at the following dose levels (DL): 1 × 10⁵ (DL1), 3 × 10⁵ (DL2), 1 × 10⁶ (DL3), 3 × 10⁶ (DL4), and 1 × 10⁷ (DL5) (FIGURE 1).

The primary end point of the trial is to identify the maximum-tolerated dose of the FSH-CER T cells. Secondary end points will include duration of response, duration of stable disease, and overall survival with this approach.

“The primary goal is safety, and we will also pay attention to some efficacy,” Conejo-Garcia said. “There will be read out to understand T-cell persistence, [and] we will be tracking in [the] blood how long these T cells persist in the patient. We will analyze the infusion product in detail to understand how the quality of the T cells that we are infusing into the patient would influence therapeutic effectiveness. We will also conduct the studies aiming to understand the effect of this intervention on preexisting antitumor immunity, because by reducing tumor burden and inducing antigen spreading, we hoped that preexisting polyclonal responses [already] operating in the [patient] would get boosted. That would provide stronger antitumor immunity that would control tumor growth more effectively.”

It has also been hypothesized that CER-T could have a positive impact in other solid tumors that overexpress FSH, because CAR T-cell therapies have not yet made any headway in those patients. “This could have a major impact on the field of gynecologic malignancies,” Conejo-Garcia said. “We want to join the fight to make CER T cells effective against solid tumors, which is the new frontier in oncology and where I think the [ovarian cancer] field is going. It has become a challenge to make CAR T cells as effective as they are for hematologic malignancies for solid tumors. We hope what we learn [will] contribute to this fight, and [hopefully this therapy] will take the lead on that.”

The trial will be piloted by lead investigator Robert Wenham, MD, MS, FACOG, FACS, who is the chair of the Gynecologic Oncology Program at Moffitt Cancer Center.

REFERENCES


MORE ON OncLive.com
Deol on CAR T-Cell Therapy in Earlier Lines of Therapy in Cancer Care
Abhinav Deol, MD, of Karmanos Cancer Center, discusses emerging data which highlight the benefits of CAR T-cell therapy in earlier treatment setting for different cancers.

WATCH NOW: bit.ly/3l4aTAF

HER2-Targeted CAR Macrophage Under Exploration in Solid Tumors With HER2 Overexpression
The safety, tolerability, and efficacy of the anti-HER2 CAR macrophage therapy, CT-0508, will be investigated in patients with solid tumors and HER2 overexpression, as part of a first-in-human phase 1 study (NCT04660929).

READ MORE AT: bit.ly/38n61CN
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.
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

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

**Keratopathy:** Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

**Visual Acuity Changes:** A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4% of patients. Changes in 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 ophthalmologic 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 the 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 13%, and Grade 4 in 0.5% per the KVA scale. 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%, and Grade 4 in 1.7%. The median time to onset of the first infusion-related event was 26.5 days. Infusion-related reactions occurred in 43% of patients 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.

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)]. Notable requirements of the BLENREP REMS include the following:

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

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

5.3 Thomobocytopenia

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

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

5.4 Infusion-Related Reactions

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

5.5 Embryo-Fetal Toxicity

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

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 216 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

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

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (2%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

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

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

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

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

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

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

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

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

- **Eye Disorders**: Photophobia, eye irritation, infective keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders**: Vomiting.
- **Infections**: Pneumonia.
- **Investigations**: Albuminuria.

### Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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

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

**Data**

**Animal Data:** Animal reproductive or developmental toxicity studies were not conducted with belanatamb mafodotin-bmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
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 75% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <upper limit of normal [ULN]) and aspartate aminotransferase (AST) >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), Ocular Toxicity

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

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

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Enzalutamide Plus ADT Demonstrates Significant Survival Benefit in mHSPC

by KYLE DOHERTY

Clinical Perspectives

TREATMENT WITH THE androgen receptor inhibitor enzalutamide (Xtandi) plus androgen deprivation therapy (ADT) significantly reduced the risk of death in patients with metastatic hormone-sensitive prostate cancer (mHSPC), according to an analysis of the phase 3 ARCHES trial (NCT02677896).

At a median follow-up of 44.6 months, patients who received enzalutamide plus ADT (n = 574) had a 34% reduction in risk of death compared with patients who received placebo plus ADT (n = 576; HR, 0.66; 95% CI, 0.53-0.81; P < .001). The median overall survival (OS) was not reached in either group.1 In the global, double-blind ARCHES trial, adult patients with mHSPC were randomly assigned 1:1 to enzalutamide 160 mg daily plus ADT or placebo plus ADT. The study population was stratified by disease volume and prior docetaxel treatment with the control arm to the experimental arm. 2

To be eligible for the trial, patients had to have an ECOG performance status of 0 or 1 and were permitted to have prior ADT and/or treatment with docetaxel (up to 6 cycles). Patients who were being treated with ADT and/or docetaxel and had disease progression prior to being randomly assigned were ineligible.2

The primary end point of the trial was radiographic progression-free survival (rPFS). Key secondary end points include prostate-specific antigen (PSA) progression, time to initiation of new antineoplastic therapy, overall response rate, and OS.1,3

The baseline patient characteristics were well balanced between the 2 cohorts. The median age in the enzalutamide plus ADT arm was 70 years (range, 46-92) and 70 years (range, 42-92) in the placebo arm. Most patients in both arms were White (81.2% and 79.9%, respectively), had an ECOG performance score of 0 (78.0% and 76.9%, respectively), and had high disease volume (61.7% and 64.8%, respectively).1

Additional efficacy results from the analysis showed that enzalutamide plus ADT displayed clinical benefit in terms of survival across subgroups evaluated (TABLE1), except among patients who had disease localized to soft tissue, placebo plus ADT was superior to enzalutamide plus ADT with a hazard ratio of 1.13 (95% CI, 0.48-2.69), results showed.1

In the final prespecified OS analysis, the estimated survival rates were 86%, 78%, and 71% with enzalutamide plus ADT at 24, 36, and 48 months, respectively. In the placebo arm, the estimated 24-, 36-, and 48-month survival rates were 82%, 69%, and 57%, respectively.1

Investigators also reported updated rPFS data and updated data for secondary efficacy end points. The median rPFS for patients who received enzalutamide plus ADT was 49.8 months (95% CI, 47.3–not estimable [NE]) compared with 38.9 months (95% CI, 28.2-46.2) among patients who received placebo (HR, 0.63; 95% CI, 0.52-0.76). Treatment with enzalutamide plus ADT also had an effect on a patient’s time to next antineoplastic therapy. Specifically, the median time to next antineoplastic therapy was not reached (95% CI, NE-NE) in the enzalutamide arm vs 40.5 months (26.3-NE) in the placebo arm (HR 0.38; 95% CI, 0.31-0.48).4

To account for any possible crossover effect, investigators performed a prespecified rank-preserving structural failure analysis. The median time to crossover from placebo to enzalutamide was 21.5 months. Of the 184 (31.9%) patients who consented to crossover 180 (31.3%) received enzalutamide. According to this analysis, the median OS was not reached (95% CI, NE-NE) with enzalutamide plus ADT vs 47.7 months (95% CI, 43.3-NE) with placebo plus ADT (HR, 0.57; 95% CI, 0.45-0.70; P < .001).

In the adjusted analysis for rPFS via investigator assessment, the median rPFS was 49.8 months (95% CI, 47.28-NE) in the enzalutamide arm vs not reached (95% CI, 23.37-NE) in the placebo arm (HR, 0.55; 95% CI, 0.44-0.67). The median time to PSA progression in this analysis was not reached (95% CI, NE-NE) in the enzalutamide arm vs 16.6 months (95% CI, 13.8-19.42) in the placebo arm (HR, 0.19; 95% CI, 0.14-0.24).1

In terms of safety, investigators reported that treatment-emergent adverse effects (TEAEs) in the enzalutamide plus ADT group were consistent with the previously known effects of long-term enzalutamide therapy. Patients in the enzalutamide plus ADT group and the placebo plus ADT group experienced TEAEs of any grade at a rate of 90.9% and 87.8%, respectively. Grade 3 or 4 TEAEs occurred at a rate of 39.2% and 27.9%, respectively. TEAEs leading to death occurred in 5.2% of patients in the experimental arm compared with 2.1% of patients in the comparator arm.1

Patients who received enzalutamide experienced a TEAE of special interest of any grade at a rate of 72.7% vs 57.0% for patients who received placebo. Common TEAEs of special interest of any grade in the enzalutamide plus ADT group included musculoskeletal events (39.0%), fatigue (32.2%), and hypertension (14.3%). In the placebo arm, common TEAEs of special interest of any grade included musculoskeletal events (29.6%), fatigue (20.6%), and hypertension (6.8%).

The study authors concluded that enzalutamide plus ADT is an effective and well-tolerated treatment option for patients with mHSPC.

TABLE. Survival by Subgroup in the ARCHES Trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median OS, months, enzalutamide plus ADT</th>
<th>Median OS, months, placebo plus ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>54.2</td>
<td>NR</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>HR, 0.58; 95% CI, 0.38-0.88</td>
<td>HR</td>
</tr>
<tr>
<td>ECOG PS of 0 at baseline</td>
<td>HR, 0.68; 95% CI, 0.54-0.87</td>
<td>HR</td>
</tr>
<tr>
<td>ECOG PS of 1 at baseline</td>
<td>HR, 0.6; 95% CI, 0.44-0.97</td>
<td>HR</td>
</tr>
<tr>
<td>Low volume of disease</td>
<td>HR, 0.66; 95% CI, 0.43-1.03</td>
<td>HR</td>
</tr>
<tr>
<td>High volume of disease</td>
<td>HR, 0.6; 95% CI, 0.52-0.83</td>
<td>HR</td>
</tr>
<tr>
<td>Disease localization at</td>
<td>HR, 1.13; 95% CI, 0.48-2.69</td>
<td>HR</td>
</tr>
<tr>
<td>baseline, soft tissue only</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; NR, not reached; OS, overall survival; PS, performance score.

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

TURN TO PAGE 50 FOR AN INTERVIEW WITH THE LEAD INVESTIGATOR ANDREW J. ARMSTRONG, MD.
Armstrong Highlights Outcomes of Final Survival Analysis of Enzalutamide plus ADT in mHSPC

by KYLE DOHERTY

THE ANDROGEN RECEPTOR (AR) inhibitor enzalutamide (Xtandi) may represent a powerful treatment option for patients with metastatic hormone-sensitive prostate cancer (mHSPC).

In an updated analysis of the phase 3 ARCHES trial (NCT02677896), investigators noted that enzalutamide added to androgen deprivation therapy (ADT) elicited significant survival benefits among patients with mHSPC. Enzalutamide plus ADT was effective across nearly every patient subgroup examined and reduced the risk of radiographic progression or death by approximately 37% (HR, 0.63; 95% CI, 0.52-0.76). Data from the study showed that the combination was also well tolerated, and no new safety signals were identified.

“According to our trial results, men who were treated with enzalutamide and ADT lived longer than those who were treated with ADT alone,” Andrew J. Armstrong, MD, MSc, said. “We saw significant benefits across all key subgroups, with improvements detected in patients with visceral disease, bone-only metastases, and soft tissue metastases.”

1. At least half of patients with metastatic prostate cancer are still being undertreated,” Andrew J. Armstrong, MD, MSc, said. “It is important to either refer your patient to an academic or specialized center where this [treatment] can be offered to extend their lives or familiarize yourself with these data so you can intelligently prescribe and safely monitor patients during this treatment. The great thing about enzalutamide is it does not require steroids. It is not immune suppressive and is very well tolerated for long periods of time with appropriate safety monitoring.”

In an interview with OncologyLive®, Armstrong, a professor of medicine, a professor in pharmacology and cancer biology at Duke University School of Medicine in Durham, North Carolina, discussed the updated results and the clinical implications of the final survival analysis of the ARCHES trial, which he coauthored.

What was the clinical rationale for initiating the ARCHES trial?

ARCHES was designed in an era when the standard of care for men with mHSPC was ADT. There were emerging data that docetaxel also extended survival. The goal of the ARCHES trial was to test whether a more potent androgen receptor blocker, enzalutamide, could delay the risk of death or progression in these men who either present with metastatic disease or who develop metastatic disease after they have had a radical prostatectomy or radiation and then have a recurrence.

ARCHES included men who were suitable for [treatment with] ADT, and we allowed prior docetaxel. This was the one of the first studies to test that subgroup; [however,] many men do not receive docetaxel or refused chemotherapy. A large part of the ARCHES population were men who chose ADT alone and were randomized to enzalutamide at 160 mg [once daily] continuously until progression.

The primary analysis for ARCHES was published approximately 3 years ago and the more recent update is the final overall survival results, which we were happy to see were positive.

What were the highlights of the final survival data in ARCHES?

I was pleasantly surprised to see that enzalutamide-treated men lived substantially longer [with] a hazard ratio of 0.66; that is highly statistically significant and clinically significant. That was seen despite crossover of 30% to 40% of men who were treated with placebo. Even before [the patients] experienced disease progression, they were offered enzalutamide. When patients’ [disease] did progress, there were commercially available drugs [such as] enzalutamide in the castrate-resistant setting or abiraterone acetate [Zytiga], which is very similar to enzalutamide. The life-prolonging benefit of early AR inhibition was seen, despite the common later use of the same drug.

This shows that early use is better before disease resistance sets in. This is really changing the paradigm of how we treat [patients with] prostate cancer. We are using these more potent therapies earlier, where you get greater efficacy [compared with] waiting for castration-resistant progression, when there’s still efficacy and a survival benefit but it is more modest and not as durable.

Survival benefit was seen across all patient subgroups in the ARCHES trial except in those with soft tissue localization at baseline. Why do you think this is, and will that affect your use of enzalutamide in this population?

There are 2 groups of patients with soft tissue metastases: men with lymph node–only metastases and the group with visceral metastases. These are relatively small subgroups in ARCHES, so they are very underpowered.

Most of the men in ARCHES had bone metastases with lymph node metastases. A small subset, less than 20%, had visceral metastases. We saw significant benefits in those patients with bone and lymph node metastases, but we did not see clear survival benefits in the visceral subgroup, [which were mostly] liver metastases. These patients are characterized as having...
high volume disease and a very poor prognosis, particularly when prostate cancer spreads into the liver. Docetaxel and ADT are now offered to these patients, and we are moving toward triplet therapy for these patients. That approach is what I would recommend for these patients who have a poor prognosis when treated with ADT alone. They [also] have a poor prognosis when treated with doublet therapy with ADT and an AR inhibitor. [There have been] very consistent poor effects with ADT and an AR inhibitor across different trials, including ARCHES.

When in the treatment course should enzalutamide be used in patients with mHSPC vs other agents such as docetaxel, abiraterone, and apalutamide (Erleada)?

When you see a patient with metastatic prostate cancer who is untreated, the first step is to start ADT [therapy]—either with a GnRH [gonadotropin] releasing hormone] agonist or antagonist—and think about treatment intensification. The vast majority of patients need treatment intensification to live longer. Patients can tolerate this very well, and it improves life expectancy. There are only [approximately] 10% of patients who are too elderly, frail, or who have too many comorbidities to justify treatment intensification.

For those men with high-volume, high-risk disease, particularly de novo metastatic disease, I would consider triplet therapy in patients who are fit for chemotherapy. That was included in [the eligibility criteria for] ARCHES, but it is relevant for many other trials now. Most patients [have] low-volume disease. If their [disease] is de novo, I would certainly consider a potent AR inhibitor such as enzalutamide, apalutamide, or abiraterone based on level 1 evidence. ARCHES is one of those trials that was very positive. I also consider treating the primary prostate tumor with radiation to prolong survival if they have de novo disease.

If they have relapsed disease, there is also a [noted] substantial delay in progression and improvement in survival. Most patients should be offered a potent AR inhibitor when it is affordable and available. In the United States, that is the vast majority of patients. Most patients should start this [treatment] within 3 months of starting their ADT. In ARCHES, that is how it was done. Within 3 months of starting ADT, they were randomized, unless they started docetaxel [plus] ADT and then it was within 6 months. It is important to think about it early and not to delay that treatment intensification.

What should clinicians be aware of when prescribing enzalutamide plus ADT in terms of safety?

Survivorship issues are very important because men are now going to be living a lot longer. We have many more men living 5-plus years. Because of that treatment intensification, they can experience more toxicities, particularly in respect to muscle health, bone health, cardiovascular risk, metabolic risks, and fragility.

What does the future hold for enzalutamide?

The ARCHES trial has now formed the backbone for new phase 3 studies. It is no longer ethical to do a placebo-controlled trial with ADT alone because we have level 1 evidence that ADT plus a potent AR inhibitor extends life.

There are some men who still desire to avoid hormonal therapy. There are some trials that are testing for example, metastasis-directed therapies without a potent AR inhibitor, but that is more experimental. We should also be testing metastasis-directed therapies with our best systemic therapies to try to eradicate low-volume or oligometastatic disease. The STAMPEDE trial [NCT00268476] is now testing [adding metastasis-directed therapies to standard of care] in a new treatment arm [and enrolling patients with] up to 5 metastatic lesions in addition to the primary [tumor].

We are also evaluating the value of immunotherapies. Lutetium Lu 177 vipivotide tetraxtan [Pluvicto] is being tested in earlier settings [such as] this hormone-sensitive setting, being layered on top of drugs [such as] ADT and enzalutamide. There are other molecularly stratified [ongoing trials] in hormone-sensitive [disease accounting for factors such as] PTEN loss using an ATP inhibitor.

The number of trials is expanding rapidly based on these successes. There are also parallel AR inhibitors that are emerging [such as] darolutamide [Nubeqa], apalutamide, abiraterone. Looking at different combinations, triplet therapy, and doublet therapy is the way things are moving.

REFERENCE

Match-Adjusted Comparison Shows Comparable Efficacy Outcomes for Axi-cel and Tisa-cel in Follicular Lymphoma

by BRITTANY LOVELY

RESULTS OF A MATCH-ADJUSTED analysis of patients with follicular lymphoma treated with axicabtagene ciloleucel (Yescarta; axi-cel) in the ZUMA-5 trial (NCT03105336) vs those treated with tisagenlecleucel (Kymriah; tisa-cel) in ELARA (NCT03568461) showed a similar efficacy profile between the 2 cellular therapies. Further, investigators reported a more favorable safety profile among those treated with tisa-cel in both the primary and sensitivity analyses presented at the 2022 Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy and the Center for International Blood and Marrow Transplant Research.1

“Tisa-cel and axi-cel have both been evaluated in pivotal phase 2 clinical trials with registration intent—ELARA and ZUMA-5, respectively—which included patients with greater than or equal to 2 prior lines of therapy and both trials demonstrated high overall response rates [ORRs] and complete responses [CRs].” Michael Dickinson, MD, said during a presentation of the data. Dickinson is lead of the Aggressive Lymphoma Disease Group within Clinical Haematology at Peter MacCallum Cancer Centre and Royal Melbourne Hospital in Australia.

“Given this clinical context, as well as promising 12-month progression-free [survival; PFS] and overall survival [OS] data, and because head-to-head comparisons between CAR [chimeric antigen receptor] T-cell products are unlikely to occur, we performed an indirect comparison of these 2 clinical trials and their CAR T interventions. The objectives of this study were to indirectly compare efficacy and safety outcomes between tisa-cel and axi-cel in relapsed or refractory follicular lymphoma using matching adjusted, indirect comparison.”

To conduct the analysis, investigators adjusted the population using individual patient-level data, using what Dickinson described as factors of convenience. “[Investigators of] both ZUMA-5 and ELARA have reported clinically relevant factors...these factors were reasonably reflective [of real-world] patients in that they were in both primary analyses and how clinicians think about prognostic factors for real-world refractory lymphoma.”

The weighting and match analysis included the following factors: age, sex, ECOG performance status, Ann Arbor tumor staging, Follicular Lymphoma International Prognostic Index score, tumor burden, number of prior lines of therapy, prior autologous stem cell transplant, and progression of disease in 24 months. Patients treated with tisa-cel in ELARA were matched to the average characteristics from aggregated summary data of those who received axi-cel in ZUMA-5.

Two analyses were performed. The primary analysis compared included patients from ELARA who received infusion and did not have exposure to bridging chemotherapy with comparable patients from ZUMA-5. The sensitivity analysis compared those in ELARA with and without exposure to bridging chemotherapy with patients from ZUMA-5.

“ELARA differed from ZUMA-5 in that it allowed bridging chemotherapy prior to CAR T-cell therapy,” Dickinson said. “We know from other studies, particularly in the large cell lymphoma setting, [that] this may select for patients with poorer prognosis disease.”

Dickinson said investigators used a data cutoff of March 20, 2020, for ZUMA-5 and a March 29, 2021, data cutoff for ELARA. Efficacy-evaluable patients were defined as those with at least 12 months’ of follow-up. Once balanced populations were achieved, investigators compared binary outcomes including ORR, CR, and safety, as well as an analysis of PFS and OS using weighted Cox proportional hazards model for hazard ratio estimation.

OUTCOMES IN THE PRIMARY ANALYSIS

The primary analysis included 50 patients from ELARA and 84 patients from ZUMA-5. The ORRs after weighting were 92.59% vs 94.05% (P < .05) and the CRs were 77.45% vs 79.76%, respectively (TABLE). Dickinson noted that these results were comparable to the results observed before weighting, which showed ORRs of 90% vs 94.05% and CRs of 70% vs 79.76% among those treated with tisa-cel and axi-cel, respectively.

PFS was also comparable between the 2 agents. After weighting, the median PFS for those who received tisa-cel was not reached (NR; 95% CI, NR-NR) vs not reached (95% CI, 23.54-NR) with axi-cel (HR, 0.90; 95% CI, 0.39-2.06; P = .81). Prior to weighting, investigators noted a hazard ratio of 1.02 (95% CI, 0.52-1.99). OS analyses were also similar in the primary analysis, with a hazard ratio of 0.33 (95% CI, 0.07-1.57) after weighting compared with 0.45 (95% CI, 0.13-1.59) prior to weighting.

The safety analysis was conducted among 53 patients from ELARA and 124 patients from ZUMA-5. Those who received tisa-cel had lower rates of cytokine release syndrome (CRS), corticosteroid and tocilizumab use for CRS, and overall incidence of neurologic events.

Specifically, the rate of any-grade CRS, corticosteroid use, tocilizumab use, and any-grade neurologic events among those who received tisa-cel were 45.52%, 2.63%, 9.59%, and 8.75%, respectively. Among patients treated with axi-cel these rates were 78.23%, 15.32%, 45.16%, and 56.45%, respectively. In terms of grade 3 events, no patients who received tisa-cel experienced grade 3 CRS compared with 6.45% of patients who received axi-cel. Further, only 0.29% of patients

### TABLE

Primary Analysis Outcomes of Axi-cel vs Tisa-cel*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tisa-cel (n = 50)</th>
<th>Axi-cel (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>92.59%</td>
<td>94.05%</td>
</tr>
<tr>
<td>CR</td>
<td>77.45%</td>
<td>79.76%</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (NR-NR)</td>
<td>NR (23.54-NR)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>HR, 0.90; 95% CI, 0.39-2.06; P = .81</td>
<td>HR, 0.33; 95% CI, 0.07-1.57</td>
</tr>
</tbody>
</table>

*Primary analysis outcomes included efficacy-evaluable patients from ELARA treated with tisa-cel who did not receive bridging chemotherapy.

![Michael Dickinson, MD](image-url)
who received tisa-cel had a grade 3 neurological event compared with 15.32% of patients who received axi-cel.

OUTCOMES IN THE SENSITIVITY ANALYSIS
In an efficacy evaluation including patients who received bridging therapy in ELARA (n = 90), results were also comparable in terms of efficacy to patients who received axi-cel in ZUMA-5 (n = 124). After weighting, the ORR was 89.77% among those who received tisa-cel vs 94.05% among those who received axi-cel. The CR rates were 75.05% and 79.76%, respectively.

In terms of survival data, the median PFS for those who received tisa-cel was not reached (95% CI, 32.8%-51.9%) following treatment with tisa-cel, compared with 15.32% of patients who experienced a grade 3 neurologic event compared with 6.45% in ZUMA-5; 0.97% of patients who received tisa-cel had a grade 3 neurologic event compared with 15.32% of patients who received axi-cel. "Future studies using long-term follow-up data from both trials or real-world data will be important for comparisons of the efficacy and safety of tisa-cel and axi-cel for the treatment of relapsed or refractory follicular lymphoma," Dickinson said.

Axi-cel Sustains Long-Term Survival Rates in Relapsed/Refractory Large B-Cell Lymphoma

by HAYLEY VIRGIL

PATIENTS WITH RELAPSED OR refractory large B-cell lymphoma (LBCL) who received axicabtagene ciloleucel (axi-cel; Yescarta) continued to experience a long-term overall survival (OS) benefit at 5-year follow-up, according to data from an analysis of the phase 2 ZUMA-1 trial (NCT02348216) presented during the 2022 Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy and the Center for International Blood and Marrow Transplant Research.

"In this updated 5-year analysis, axi-cel induced long-term OS," according to Caron A. Jacobson, MD, MMSc, medical director of the Immune Effector Cell Therapy Program and senior physician at Dana-Farber Cancer Institute in Boston, Massachusetts. "Between the 4-year and 5-year analysis, the time to next therapy curve remains stable and 92% of patients remained alive without a need for subsequent therapy, which may be suggestive of a cure in these patients," said Jacobson.

Investigators reported a 5-year OS rate of 42.6% (95% CI, 32.8%-51.9%) following treatment with axi-cel (n = 101). In the population of patients who experienced a complete response, the 5-year OS rate was 64.4% (95% CI, 50.8%-75.1%) and the median OS was not reached (95% CI, 63.4-not estimable). Additionally, 63% of complete responders were alive at the 5-year data cut off.

To be considered for treatment, patients were required to have LBCL, including diffuse LBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma. Patients were also required to have not responded to their last chemotherapeutic or have relapsed 12 months or less following autologous stem cell transplant. Treatment with a previous anti-CD20 monoclonal antibody and anthracycline was also required.

Those who underwent treatment received a conditioning regimen of cyclophosphamide at 500 mg/m² and 30 mg/m² of fludarabine for 3 days. This was followed by axi-cel at a dose of 2 × 10⁶ CAR T cells/kg. The primary end point was overall response rate with first response assessment 4 weeks following infusion. Key secondary end points included OS, safety, and translational evaluations.

A total of 111 patients were enrolled in the study, and 103 received infusion. Reasons why patients did not undergo treatment included adverse effects (AEs; n = 4), no measurable disease (n = 2), death due to disease progression (n = 1), and manufacturing failure (n = 1). The median follow-up was 63.1 months.

Additional findings from the trial highlighted a median time to next anticancer therapy of 8.7 months following infusion. A total of 34% of patients were alive at the cutoff with no subsequent therapy or retreatment with axi-cel. Two patients who had prior progression underwent new anticancer therapy. According to results of an exploratory analysis, investigators reported that 1-year and 2-year event-free survival (EFS) may potentially have a role as a surrogate end point for long-term OS.

The 5-year OS rates among those who had or had not experienced an EFS event at month 12 were 5.3% vs 90.9%, respectively. The median OS was 8.3 months among those who experienced an event and was not reached in those who did not experience an event. Additionally, the 5-year OS rates among those who did or did not have an EFS event at month 24 were 11.3% and 92.3%, respectively. Moreover, the median OS in both respective groups was 9.2 months and not reached.

Investigators also determined that early CAR T-cell expansion was associated with ongoing response at 60 months. The median peak CAR T levels appeared to be numerically higher in those who had an ongoing response at month 60 and lower in those who relapsed or did not respond to treatment. Similarly, another trend was observed in those who experienced CAR T-cell expansion by area under the curve from day 0 to 28.

A total of 58% of patients had died by the cutoff date. No new safety signals had been observed as of the 5-year data cutoff, including serious AEs or secondary malignancies related to treatment.

REFERENCE
Liso-cel Exhibits Durable Responses in Relapsed/Refractory LBCL

by HAYLEY VIRGIL

AT A 2-YEAR FOLLOW-UP, lisocabtogene maraleucel (liso-cel; Breyanzi) continued to yield positive outcomes in patients with relapsed/refractory large B-cell lymphomas (LBCLs), according to results from the phase 1 TRANSCEND NHL 001 trial (NCT02631044) presented during the 2022 Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy and the Center for International Blood and Marrow Transplant Research.1

Treatment with liso-cel elicited an overall response rate (ORR) of 73% (95% CI, 66.9%-78.1%), including a complete response (CR) rate of 53% (95% CI, 46.6%-59.2%) among 257 efficacy-evaluable patients after a median follow-up of 23.0 months. The median duration of response (DOR) by Lugano 2014 criteria was 23.1 months (95% CI, 8.6-not reached [NR]) and the probability of continued response at 2 years was 49.5% (95% CI, 41.4%-57.0%).2 Additionally, the median DOR was 26.1 months (95% CI, 23.1-NR) and 23.1 months (95% CI, 5.6-NR) in those who achieved a CR and partial response (PR), respectively.

“This 2-year follow-up analysis of TRANSCEND demonstrated durable response to liso-cel in patients with high-risk aggressive relapsed/refractory LBCLs,” Jeremy Abramson, MD, director of the Jon and Jo Ann Hagler Center for Lymphoma, Massachusetts General Hospital, and an associate professor of medicine at Harvard Medical School in Boston, Massachusetts, said during the presentation. “Liso-cel treatment was associated with a low incidence of severe cytokine release syndrome [CRS] and neurologic events,” Abramson added.

To be eligible for the study, patients needed to be 18 years or older and have received 2 or more prior lines of therapy. Those who enrolled had diffuse large B-cell lymphoma that was not otherwise specified (DLBCL NOS)—either de novo or transformed from follicular lymphoma, marginal zone lymphoma, or another disease—high-grade B-cell lymphoma (HGBCL), primary mediastinal LBCL (PMLBCL), or follicular lymphoma grade 3B (FL3B). Other inclusion criteria included previous hematopoietic stem cell transplant and an ECOG performance status of 0 or 2. Primary central nervous system lymphoma was also allowed.

Patients received a lymphodepleting regimen of 30 mg/m² fludarabine and 300 mg/m² of cyclophosphamide for 3 days followed by liso-cel 2 to 7 days later. The on-study follow-up was 24 months.

The study’s primary end points were adverse effects (AEs) and ORR by independent review committee. Secondary end points included CR rate by IRC, DOR, progression-free survival (PFS), overall survival (OS), and pharmacokinetic profile. Patients who enrolled in the trial were followed for 2 years after the last liso-cel dose, and the study was ongoing as of the cutoff date of January 2021. Also, 268 patients had died or withdrawn 24 months or more after follow-up. Among 120 patients who completed the study, 81 agreed to be part of a long-term follow-up study assessing safety and OS up to 15 years.

Notably, 1 patient died following an ongoing CR at 26 weeks due to sepsis. No patients relapsed after 23 months in the study.

The median patient age was 63 years and 41% of patients were 65 years or older. The majority of patients had DLBCL NOS (51%); others had transformed follicular lymphoma (22%), other indolent lymphomas (7%), HGBCL (13%), PMLBCL (6%), and FL3B (1%). Additionally, most patients were chemotherapy refractory (67%) and underwent treatment with a bridging therapy (59%). The overall median follow-up was 19.9 months.

Additional findings from the study indicated that after a median follow-up of 23.9 months, the median PFS was 6.8 months (95% CI, 3.3-12.7) and the probability of PFS at 2 years was 40.6% (95% CI, 34.0%-47.2%). The median PFS in those who had a CR was 27.3 months (95% CI, 24.0-NR) and 6.8 months (95% CI, 3.3-12.7) in those who had a PR.

After a median follow-up of 29.3 months, the median OS was 27.3 months (95% CI, 16.2-45.6), with a 2-year probability of OS rate of 50.5% (95% CI, 44.1%-56.5%). The median OS in those who had a CR or PR was 48.5 months (95% CI, 45.2-NR) and 9.0 months (95% CI, 6.0-11.4), respectively. In nonresponders, the median OS was 5.4 months (95% CI, 2.9-6.5). Three deaths occurred after 45 months. Moreover, CAR T-cell persistence was detected at 48 months in the long-term follow-up study (NCT03433796) in addition to 37% of patients at 24 months in the TRANSCEND study.

In terms of safety, the most common any-grade AEs within 90 days of infusion were neutropenia (63%), anemia (48%), and fatigue (44%); grade 3 or higher AEs included neutropenia (60%), anemia (37%), and thrombocytopenia (27%). Any-grade and grade 3 or higher infections occurred in 12% of patients, and in 41% of patients with any-grade AEs. From day 91 to the end of study, the most common any-grade AEs were neutropenia (8%), anemia (8%), and fatigue (7%), with grade 3 or higher AEs including neutropenia (7%), anemia (6%), and thrombocytopenia (4%). Any-grade and grade 3 or higher infections occurred in 5% of patients, and in 10% of patients with any-grade AEs.

Investigators reported several AEs of special interest. Any-grade and grade 3/4 CRS were reported in 42% and 2% of patients, respectively; the median time to onset and resolution of CRS was 5 days. Any-grade and grade 3/4 neurologic events were reported in 30% and 10% of patients, respectively. The median time to onset was 9 days and the median time to resolution was 11 days. Most cases of CRS and neurologic events were grade 1/2, with no grade 5 events.

Second primary malignancies (SPMs) occurred in 5 and 17 patients during the treatment emergent and posttreatment emergent periods, respectively. The types and incidence of SPMs were expected given the patient population and prior therapies and included diseases such as nonmelanoma skin cancer (n = 9), solid tumors (n = 4), myelodysplastic syndrome (n = 8), acute myeloid leukemia (n = 2), and peripheral T-cell lymphoma (PTCL; n = 1). The single case of PTCL was reported on day 30 and did not appear to be related to treatment with liso-cel.

Of 270 patients, 9 died 30 days or less following last infusion; 24 died at over 30 days to 90 days or less; and 100 died at over 90 days.

REFERENCES
KISQALI® (ribociclib) is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

**MONALEESA-2, a dedicated 1L postmenopausal trial:** At a median follow-up of 80 months, median OS was 63.9 months with KISQALI® (ribociclib) + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); P=0.004. In the primary analysis at a median follow-up of 15 months, mPFS was not reached (95% CI: 19.3-NR) vs 14.7 months (95% CI: 13.0-16.5); HR=0.556 (95% CI: 0.429-0.720); P<0.0001.

**Indications**

KISQALI® (ribociclib) is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

**IMPORTANT SAFETY INFORMATION**

**Interstitial lung disease/pneumonitis.** Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors. Across clinical trials in patients with advanced or metastatic breast cancer treated with KISQALI in combination with an aromatase inhibitor or fulvestrant (“KISQALI treatment groups”), 1.1% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.3% had grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.
KISQALI is the only CDK4/6 inhibitor with statistically significant overall survival data reported in postmenopausal patients with an AI.

See Dr Gabriel Hortobagyi share his perspectives on the data. “What this particular clinical trial has achieved… is an enormous step forward.” —Gabriel Hortobagyi, MD

**IMPORTANT SAFETY INFORMATION (continued)**

**Interstitial lung disease/pneumonitis (continued).** Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis.

**Severe cutaneous adverse reactions.** Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DRESS) have been reported in patients treated with KISQALI in the postmarketing setting. If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.
The longest median overall survival ever reported in HR+/HER2- mBC

MONALEESA-2: KISQALI + AI in 1L postmenopausal patients
At a median follow-up of 80 months

OVERALL SURVIVAL | KISQALI + AI

![Graph showing overall survival comparison between KISQALI + AI and Placebo + AI]

- **63.9 months mOS** (95% CI: 52.4-71.0) for KISQALI + AI
- **51.4 months mOS** (95% CI: 47.2-59.7) for Placebo + AI

**Hazard ratios are based on stratified Cox model.**

OVERALL SURVIVAL BENEFIT WITH KISQALI INCREASED OVER TIME

At 6 years, the survival rate of patients receiving KISQALI® (ribociclib) + letrozole was 44% vs 32% with placebo + letrozole.

**PFS:** In the primary analysis, at a median follow-up of 15 months, mPFS was not reached with KISQALI + letrozole (95% CI: 19.3-NR) vs 14.7 months with placebo + letrozole (95% CI: 13.0-16.5); HR=0.556 (95% CI: 0.429-0.720); \(P<0.0001\). In an updated analysis with a median follow-up of 26 months, mPFS was 25.3 months (95% CI: 23.0-30.3) vs 16.0 months (95% CI: 13.4-18.2).\(^3-5\)

**Study design:** MONALEESA-2 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + letrozole (n=334) vs placebo + letrozole (n=334) in postmenopausal patients with HR+/HER2- mBC who received no prior therapy for advanced disease. OS was a secondary end point; PFS was the primary end point.\(^3,4\)

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

Severe cutaneous adverse reactions (continued). If SCARs is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 14 of 1054 patients (1%) had >500 ms postbaseline QTcF value, and 59 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:
- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the NSAI + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Hepatobiliary toxicity. Across clinical trials in patients with advanced or metastatic breast cancer, increases in transaminases were observed. Across all trials, grade 3 or 4 increases in alanine aminotransferase (ALT) (10% vs 2%) and aspartate aminotransferase (AST) (7% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 85 days and median time to resolution to grade ≤2 was 22 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.
**Neutropenia.** Across trials, neutropenia was the most frequently reported adverse reaction (AR) (74%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 16 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 0.8%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

**Embryofetal toxicity.** Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryofetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

**Adverse reactions.** Across clinical trials of patients with advanced or metastatic breast cancer, the most common ARs reported in the KISQALI treatment groups (pooled incidence ≥20%) were neutropenia (74% vs 5%), nausea (45% vs 27%), infections (41% vs 30%), fatigue (33% vs 30%), diarrhea (30% vs 22%), leukopenia (30% vs 3%), vomiting (27% vs 16%), alopecia (24% vs 12%), headache (24% vs 22%), constipation (24% vs 16%), rash (21% vs 9%), and cough (21% vs 16%). The most common grade 3/4 ARs (reported at a pooled frequency >5%) were neutropenia (59% vs 1%), leukopenia (16% vs 3%), abnormal LFTs (9% vs 2%), and lymphopenia (5% vs 1%).

**Laboratory abnormalities.** Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm vs placebo arm (all grades, pooled incidence ≥20% and ≥5% higher than placebo arm) were leukocyte count decrease (94% vs 30%), neutrophil count decrease (93% vs 25%), hemoglobin decrease (66% vs 38%), lymphocyte count decrease (61% vs 26%), AST increase (47% vs 38%), ALT increase (44% vs 36%), creatinine increase (38% vs 13%), and platelet count decrease (31% vs 9%). The most common grade 3/4 laboratory abnormalities (incidence >5%) were neutrophil count decrease (59% vs 2%), leukocyte count decrease (32% vs 1%), lymphocyte count decrease (15% vs 4%), ALT increase (10% vs 2%), and AST increase (7% vs 2%).

1=first line; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; ET=endocrine therapy; HR=hazard ratio; mBC=metastatic breast cancer; mOS=median overall survival; mPFS=median progression-free survival; NR=not reached; OS=overall survival; PFS=progression-free survival.

KISQALI® (ribociclib) tablets, for oral use

**INDICATIONS AND USAGE**

KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

Across clinical trials (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.1% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.3% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported [see Adverse Reactions (6.2)].

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis [see Dosage and Administration (2.2) in the full prescribing information].

5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI [see Adverse Reactions (6.2)].

If signs or symptoms of severe cutaneous reactions occur, interrupt KISQALI until the etiology of the reaction has been determined [see Dosage and Administration (2.2) in the full prescribing information]. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce ribociclib in patients who have experienced SCARs or other life threatening cutaneous reactions during KISQALI treatment.

5.3 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner [see Clinical Pharmacology (12.2) in the full prescribing information]. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 [see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.4)].

Across MONALEESA-2, MONALEESA-7, and MONALEESA-3, in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (1%) had a > 50 ms post-baseline QTc value, and 59 out of 1054 patients (6%) had a > 60 ms increase from baseline in QTc intervals.

These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, on the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 [see Adverse Reactions (6.5)].

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTc values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy [see Dosage and Administration (2.2) in the full prescribing information].

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTc interval.

5.4 Increased QT Prolongation With Concomitant Use of Tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTc increase with KISQALI alone was > 10 ms higher in the tamoxifen plus placebo subgroup compared with the non-steroidal aromatase inhibitors (NSAIs) plus placebo subgroup. In the placebo arm, an increase of > 60 ms from baseline occurred in 6/98 (7%) of patients receiving tamoxifen, and in no patients receiving a NSAI. An increase of > 80 ms from baseline in the QTc interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI [see Clinical Pharmacology (12.2) in the full prescribing information].

5.5 Hepatobiliary Toxicity

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, Grade 3 or 4 increases in alanine aminotransferase (ALT) (10% vs. 2%) and aspartate aminotransferase (AST) (7% vs. 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT failure, the median time-to-onset was 85 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≥ 2 was 22 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the upper limit of the normal range occurred in at least one of the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated [see Dosage and Administration (2.2) in the full prescribing information].

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobility Toxicity) [see Dosage and Administration (2.2) in the full prescribing information]. Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

5.6 Neutropenia

In MONALEESA-2, MONALEESA-7, and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (74%), and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was seen in 58% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 to normalization or Grade ≤ 3 was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in 1% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 0.8%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6 [see Dosage and Administration (2.2) in the full prescribing information].

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose [see Use in Specific Population (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information].

**ADVERSE REACTIONS**

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

- **Interstitial Lung Disease/Pneumonitis** [see Warnings and Precautions (5.1)]
- **Severe Cutaneous Adverse Reactions** [see Warnings and Precautions (5.2)]
- **QT Interval Prolongation** [see Warnings and Precautions (5.3, 5.4)]
- **Hepatobiliary Toxicity** [see Warnings and Precautions (5.5)]
- **Neutropenia** [see Warnings and Precautions (5.6)]

5.8 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.

MONALEESA-2, MONALEESA-3 in Combination with Letrozole

Table 8: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-7 (All Grades)

<table>
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<tr>
<th>Adverse Drug Reactions</th>
<th>All Grades</th>
<th>Placebo + Letrozole</th>
<th>Placebo + NSAI + Goserelin</th>
<th>Placebo + NSAI + goserelin</th>
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(continued)
MONALEESA-2: KISQALI in Combination with an Aromatase Inhibitor
Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

MONALEESA-2 was conducted in 872 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure on the KISQALI arm was 15.2 months with 66% of patients exposed for ≥12 months. The safety data reported below are based on 495 pre/perimenopausal patients receiving KISQALI plus letrozole or placebo plus letrozole. Dose reductions due to ARs occurred in 33% of patients receiving KISQALI plus letrozole, and in 4% of patients receiving placebo plus letrozole. Among patients receiving KISQALI plus letrozole, 3% were reported to have permanently discontinued both KISQALI and NSAI and 3% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus letrozole, 2% were reported to have permanently discontinued both places and 0.8% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation on KISQALI in patients receiving KISQALI plus letrozole (as compared to the placebo arm) were ALT increased (2% vs. 0.8%), AST increased (2% vs. 0.8%), drug-induced liver injury (1% vs. 0.4%). One patient (0.4%) died while on treatment with KISQALI plus letrozole due to the underlying malignancy.

The most common ARs (reported at a frequency ≥20% on the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, arthralgia, nausea, and alopecia. The most common Grade 3/4 ARs (reported at a frequency ≥5%) were neutropenia, leukopenia, and abnormal liver function tests. See Table 10 below.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-2 are listed in Table 10 and Table 11, respectively.

---

Table 8: Adverse Reactions Occurring in ≥10% and ≥2% Higher Than Placebo Arm in MONALEESA-2 (All Grades)

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>KISQALI + letrozole</th>
<th>Placebo + letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td><strong>General Disorders and Administration-site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

1) Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

---

Table 9: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-2

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + letrozole</th>
<th>Placebo + letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count decreased</td>
<td>93</td>
<td>31</td>
</tr>
<tr>
<td>Neutrophil decreased</td>
<td>93</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>29</td>
<td>1</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

1) Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

---

Table 10: Adverse Reactions Occurring in ≥10% and ≥2% Higher Than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>KISQALI + NSAI + goserelin</th>
<th>Placebo + NSAI + goserelin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79</td>
<td>55</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td><strong>General Disorders and Administration-site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

1) Infections: urinary tract infections; respiratory tract infections; gastrointestinal; sepsis (<1%).

---

Table 11: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-7

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + NSAI + goserelin</th>
<th>Placebo + NSAI + goserelin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count decreased</td>
<td>93</td>
<td>34</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>92</td>
<td>54</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>84</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>26</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

1) Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

---

MONALEESA-3: KISQALI in Combination with Fulvestrant
Postmenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy or After Disease Progression on Endocrine Therapy

The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months until 55% of patients exposed for ≥12 months. Dose reductions due to ARs occurred in 32% of patients receiving KISQALI plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Among patients receiving KISQALI plus fulvestrant, 8% were reported to have permanently discontinued both KISQALI and fulvestrant and 9% were reported to have discontinued KISQALI alone due to ARs. Among patients receiving placebo plus fulvestrant, 4% were reported to have permanently discontinued both and 2% were reported to have discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus fulvestrant (as compared to the placebo arm) were ALT increased (5% vs. 0%), AST increased (3% vs. 0.6%), and vomiting (1% vs. 0%).

On-treatment deaths, regardless of causality, were reported in seven patients (1.4%) due to the underlying malignancy and six patients (1.2%) due to other causes while on treatment with KISQALI plus fulvestrant. Causes of death included one pulmonary embolism, one acute respiratory distress syndrome, one cardiac failure, one pneumonia, one hemorrhagic shock, and one ventricular arrhythmia. Seven patients (2.9%) died due to the underlying malignancy and one patient (0.4%) died due to pulmonary embolism while on placebo plus fulvestrant.

The safety data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months until 55% of patients exposed for ≥12 months. Dose reductions due to ARs occurred in 32% of patients receiving KISQALI plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Among patients receiving KISQALI plus fulvestrant, 8% were reported to have permanently discontinued both KISQALI and fulvestrant and 9% were reported to have discontinued KISQALI alone due to ARs. Among patients receiving placebo plus fulvestrant, 4% were reported to have permanently discontinued both and 2% were reported to have discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus fulvestrant (as compared to the placebo arm) were ALT increased (5% vs. 0%), AST increased (3% vs. 0.6%), and vomiting (1% vs. 0%).

On-treatment deaths, regardless of causality, were reported in seven patients (1.4%) due to the underlying malignancy and six patients (1.2%) due to other causes while on treatment with KISQALI plus fulvestrant. Causes of death included one pulmonary embolism, one acute respiratory distress syndrome, one cardiac failure, one pneumonia, one hemorrhagic shock, and one ventricular arrhythmia. Seven patients (2.9%) died due to the underlying malignancy and one patient (0.4%) died due to pulmonary embolism while on placebo plus fulvestrant.

---

Table 12: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-3

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + NSAI + goserelin</th>
<th>Placebo + NSAI + goserelin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count decreased</td>
<td>93</td>
<td>34</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>92</td>
<td>54</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>84</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>26</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.
The most common ARs (reported at a frequency ≥20% on the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. The most common Grade 3/4 ARs (reported at a frequency ≥5%) were neutropenia, leukopenia, infections, and abnormal liver function tests. See Table 12.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 12 and Table 13, respectively.

### Table 12: Adverse Reactions Occurring in ≥10% and ≥2% Higher Than Placebo Arm in MONALEESA-3 (All Grades)

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>KISQALI + fulvestrant N = 483</th>
<th>Placebo + fulvestrant N = 241</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Infections</td>
<td>42%</td>
<td>30%</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>69%</td>
<td>46%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27%</td>
<td>12%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>13%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>45%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27%</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>25%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Rash</td>
<td>23%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>General Disorders and Administration-site Conditions</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>13%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

1 Infections: urinary tract infections, respiratory tract infections, gastrointestinal, sepsis (<1%).

### Table 13: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-3

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + fulvestrant N = 483</th>
<th>Placebo + fulvestrant N = 241</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Leukocyte count decreased</td>
<td>95%</td>
<td>25%</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>92%</td>
<td>46%</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>60%</td>
<td>4%</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>69%</td>
<td>14%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>33%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>65%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>52%</td>
<td>6%</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>49%</td>
<td>5%</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>44%</td>
<td>8%</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Phosphorous decreased</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Grading according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

Additional adverse reactions in MONALEESA-3 for patients receiving KISQALI plus fulvestrant included asthenia (14%), dyspepsia (10%), thrombocytopenia (9%) dry skin (8%), dysgeusia (7%), dry mouth (5%), vertigo (5%), dry eye (5%), larcination increased (4%), erythema (4%), hypocalcemia (4%), bilirubin increased (1%), syncope (1%), interstitial lung disease (0.4%), pneumonitis (0.4%), hypersensitivity pneumonitis (0.2%), and acute respiratory distress syndrome (0.2%).

### 7 Drug Interactions

#### 7.1 Drugs That May Increase Ribociclib Plasma Concentrations

- CYP3A4 Inducers
  - Concomitant use of strong CYP3A4 inducers (e.g., rifampin, rifaximin, or efavirenz) may lead to reduced concentration of ribociclib.
  - Avoid concomitant use of strong CYP3A4 inducers and other drugs that are known to prolong the QT interval.

#### 7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

- CYP3A4 Inhibitors
  - Avoid concomitant use of CYP3A4 inhibitors with a narrow therapeutic index, including but not limited to itraconazole, ketoconazole, troleandomycin, clarithromycin, and ritonavir.

#### 7.3 Effect of KISQALI on Other Drugs

- CYP3A Substrates with Narrow Therapeutic Index
  - Avoid concomitant use of CYP3A substrates with a narrow therapeutic index, including but not limited to verapamil, diltiazem, and quinidine.

#### 8 Use in Specific Populations

##### 8.1 Pregnancy

- Risk Summary
  - Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.3) in the full prescribing information].

- There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of post implantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/kg/day based on AUC [see Dosage and Administration (2.2) in the full prescribing information].

- Avoid exposure to ribociclib during pregnancy [see Non-Radioactive Breastfeeding (8.6) in the full prescribing information].

- Breastfeed women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

- It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on breastfeeding infants.

### 8.2 Lactation

- Risk Summary
  - Ribociclib is present in human milk. Pregnancy: Breastfeeding women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.
8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A), a reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) [see Dosage and Administration (2.2) in the full prescribing information]. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{0-24}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{0-24}) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

8.7 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73 m² < estimated glomerular filtration rate [eGFR] < 90 mL/min/1.73 m²) or moderate (30 mL/min/1.73 m² < eGFR < 60 mL/min/1.73 m²) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m²), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information].

10 OVERDOSAGE

There is limited experience with reported cases of overdose with KISQALI in humans. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.
Innovations in Patient-Reported Outcomes Lead to Better Care

by KYLE DOHERTY

FOR DECADES IN CANCER CARE, the compiling of patient-reported outcomes (PROs) was limited to simple standardized questionnaires completed with pen and paper. They were designed to give clinicians a general idea of how a diagnosis of cancer and the corresponding treatment regimen affected patients mentally and physically. However, the collection of PROs and their application to treatment decisions has rapidly evolved over recent years, leading to more personalized and effective treatment regimens for patients with cancer.

“PROs are where a question is asked of the patient and the patient responds in an unassisted way,” said Ishwaria M. Subbiah, MD, MS, a medical oncologist and palliative care and integrative medicine physician at The University of Texas MD Anderson Cancer Center (MD Anderson) in Houston, in an interview with OncologyLive®.

PROs encompass a wide variety of signs, symptoms, and feelings. Examples in clinical oncology practice include the measuring of pain, daily activity levels, appetite, and dietary habits, among many others, with new innovations making their reporting more accurate, instantaneous, and clinically effective.

PRO INNOVATIONS AFFECTING CLINICAL PRACTICE AND OUTCOMES

The telehealth revolution spurred by the COVID-19 pandemic has touched nearly every aspect of cancer care and health care in general, and PROs are no exception. Mobile apps, online platforms, artificial intelligence–driven algorithms, and other innovations aimed at gathering PROs in a more convenient way for patients and clinicians are becoming commonplace.

“Technology has penetrated health care in a way that is unprecedented when it comes to the patients,” Subbiah said. “On the back end, as clinicians, we have seen how technological advances change how we deliver health care, as well as how we transmit information amongst clinical teams and across institutions.”

An effective new entry in PRO collection has been the Adverse-events: Patient Information and aDvice (eRAPID) system. eRAPID is designed to provide patients with a secure online platform that is accessible from their home computer or other internet-capable device. The system is programmed with an automated clinical algorithm which delivers advice for symptom management or a prompt to call for assistance based on symptom severity.1

Investigators evaluated eRAPID in a phase 3 trial (ISRCTN88520246) in combination with standard care in 508 patients with mostly early-stage cancers who were being treated with curative intent. The trial included patients with colorectal, breast, or gynecological cancers who were planning to receive chemotherapy and had internet access. The investigators randomly assigned the patients 1:1 to receive either standard care (n = 252) or standard care plus eRAPID (n = 256).

In the study, standard care included receiving verbal and written treatment information during in-person visits with an oncologist, regular assessment via telephone or in clinic, and contact with the hospital using an emergency hotline. Patients in the experimental arm completed online symptom-related questions from home over a period of 18 weeks, with weekly reminders being sent via text message and email. The patients’ symptom reports were relayed to their care team in real time using an electronic patient records system.

The primary end point of the trial was symptom control assessed by the Functional Assessment of Cancer Therapy-General, Physical Well-Being subscale at 6, 12, and 18 weeks. Secondary end points included processes of care, patient self-efficacy, and quality of life.

Results from the trial showed that eRAPID had a significant effect on improving patient physical well-being and self-efficacy and did not lead to a significant increase in hospital workload. eRAPID use led to improvement in physical well-being compared with usual care at 6 weeks (P = .028) and 12 weeks (P = .039). Patients who used eRAPID also had less clinically meaningful deterioration of physical well-being at 12 vs patients who received usual care (47% vs 56%).

The average patient adherence with weekly symptom reporting was 64.7%. Although eRAPID participation was not associated with a difference in process of care, patients who used the intervention reported better overall health-related quality of life by the EQ visual analogue scale at 12 weeks (P = .0095) and 18 weeks (P = .0302) compared with those who received usual care (TABLE1).

“PROs are impactful when they measure symptoms,” Subbiah said. “Where the impact has truly been dramatic is when patients are asked this question remotely between clinic visits when they are not face to face with a health care team member. Through remote symptom monitoring, patients can mark how they are doing specifically when it was yesterday, or a week ago, or 2 weeks ago. This is important because then you can pick up changes in how they are doing when the change is subtle vs when it is more severe.”

PRO reporting systems designed specifically for mobile devices have also gained traction as smartphones have become increasingly commonplace among patients of all ages. One such app is...
SeamlessMD, a Health Insurance Portability and Accountability Act-compliant cloud-based platform that enables clinicians to provide patients with education and symptom monitoring services that patients can access via their smartphone.¹

Kneuer et al tested the utility of SeamlessMD for patient engagement and PRO assessment following robotic surgery for lung cancer. The app was customized to cater to the requirements of the thoracic enhanced recovery pathway and included measures for preoperative preparation, in-hospital recovery, and postoperative discharge care.

The study included 50 adult patients with a diagnosis of or suspected lung cancer who were scheduled for robotic lung resection. SeamlessMD was made available on Apple and Android devices and the study allowed patients to designate a proxy, such as a spouse or child, if they were unable to use the app by themselves. Questions and tasks prompted on SeamlessMD were personalized to the needs of the individual patient and included daily symptom assessments, educational materials, exercise regimens, and recovery progress checks. Of 20 patients who returned the preoperative adherence survey, 85% reported receiving wound education and 95% adhered to some or all of the daily exercise programs. The postoperative health reports were completed by 27 patients, with a median of 3 (range, 0-17) completed surveys per patient.

Results from the postoperative health checks showed that the intervention was effective at improving patients’ confidence in their treatment regimen: 85.2% of patients reported improved confidence and 81.5% expressed increased levels of worrying after completing the checks. A significant number of patients (40.9%) also said that the app’s health checks helped them avoid 1 or more phone calls to their care team, and 18.2% of patients said the checks helped them avoid at least 1 hospital visit.

Overall, patient satisfaction with SeamlessMD was high; 74.2% of patients who completed the preoperative survey (n = 31) found the app very helpful in terms of preparing themselves for their procedure. Among patients who completed the in-hospital survey (n = 31), 74.2% found the app extremely useful or very useful while they were in the hospital. Finally, after discharge, most of the 33 patients who were surveyed (78.8%) found SeamlessMD extremely or very useful post discharge and all patients said they would definitely or probably recommend the app.

"There are many third-party applications that are in this space," Subbiah noted. "The common theme [among those] is they want it to be as user friendly as possible for the patients. They want to ask good questions so that you get answers that, as a clinical team member, [you can] actually interpret and use.”

Effectively applying PRO measures, both new and old, is not without its challenges for clinicians, patients, and institutions. According to Subbiah, factors such as a patient’s comfort level with and access to necessary technology, accuracy in the self-reporting of symptoms, and the variety and differences among PRO collection methods all serve as potential barriers to effectively harnessing PROs.

To address some of the challenges presented by PROs, MD Anderson formed the Patient Survey Informatics Committee, which Subbiah chairs. The committee is tasked with overseeing the implementation of PROs across the institution and applying them to clinical practice and grew out of a need for remote symptom monitoring oversight and guidance.

Oncologists, patient experience team members, patient educators, clinical nurses, and legal team members all have a presence on the Patient Survey Informatics Committee, Subbiah noted. He added that the committee works to refine how questions are presented to patients, ensure with clinicians that questions are clinically validated, avoid question redundancy, and optimize workflows related to PROs.

THE NEXT STEP FOR PROs

According to Subbiah, a major innovation ongoing in the realm of PROs is their increasing synchronicity with biometric data. By definition, PROs are written responses; however, Subbiah argues that dynamic PRO capture methods that take into account changes the patient may not immediately recognize themselves can increase the speed and quality of care.

"[PROs] can be patients answering [questions but can also include] wearing a sensor, monitor, or watch device that has biometric [capabilities],”

**TABLE. Self-Efficacy and QOL Outcomes**¹

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>eRAPID plus usual care (n = 256)</th>
<th>Usual care (n = 252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-item self-efficacy scale (range, 1-10; high score = high self-efficacy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean at baseline</td>
<td>6.85</td>
<td>6.74</td>
</tr>
<tr>
<td>Mean at week 18</td>
<td>7.55</td>
<td>6.96</td>
</tr>
<tr>
<td>Patient activation measure (range, 0-100; high score = higher activation)</td>
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</tr>
<tr>
<td>Mean at baseline</td>
<td>66.7</td>
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<tr>
<td>Mean at week 18</td>
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<td>63.5</td>
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<tr>
<td>EQ5D-VAS (range, 0-100; high score = best possible health)</td>
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<tr>
<td>Mean at baseline</td>
<td>76.3</td>
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<tr>
<td>Mean at week 18</td>
<td>75.6</td>
<td>68.7</td>
</tr>
</tbody>
</table>

³eRAPID, electronic patient self-reporting of adverse events; Patient Information and Advice; EQ VAS, EuroQol visual analogue scale; QOL, quality of life.

³Subbiah said, “Clinicians can get objective information [such as] step counts, activity levels, sleep quality, heart rate, oxygen levels, and blood pressure. [The goal is] to get information on how a patient is doing when they are not right in front of you. We know things change; we know health is dynamic.”

One such measure that combines traditional PROs with biometric data was tested in the HOPE pilot study (NCT03022032). Ten patients with gynecologic cancers who received palliative chemotherapy wore accelerometers to evaluate their physical activity. To record PROs, investigators used the Beiwe research platform, which monitors activity passively using a smartphone’s sensor to trigger surveys. This enabled data to be collected without any direct involvement from the patient, in addition to the PROs filled out by patients.

Results showed that the combination of PROs and active monitoring of patients’ heart rates and daily steps identified patient behavior patterns and suggested poor health in 2 patients. Specifically, drops in step patterns and disruptions in circadian behavior were observed in a patient who had severe nausea and vomiting. The system prompted a survey from the care team and the patient was contacted to manage symptom burden at home.

Most patients (n = 9) said they would recommend the app to a friend going through treatment. Clinicians and patients also reported that the HOPE study had a positive effect on the physical activity of patients, communication, and symptom management.

"[PROs] are an area of rapid evolution; it is one of the exciting areas [in cancer care],” Subbiah said. "A patient’s health and well-being are not static between clinic visits; we know that change has happened. The key is innovation that captures those changes as early as possible. [PROs and biometric data] have independently existed for years, but merging them, interpreting them, and correlating that merger with clinical outcomes—that is new and exciting.”

³For a full list of references, see the article at OncLive.com
Molecular Approaches May Increase Responsiveness to Immunotherapy for Patients With Metastatic Melanoma

by ALAN J. TACKETT, PhD; AND NATHAN L. AVARITT, PhD

CUTANEOUS MELANOMA IS THE deadliest form of skin cancer with incidence rates increasing each year. Historically, treatment options for patients with metastatic melanoma have been limited, and 5-year survival rates were less than 10% for patients with advanced-stage disease.

However, the recent development of therapeutics which stimulate immune response to tumor cells has revolutionized the treatment landscape for this disease. But although some patients experience a durable response to these treatments, others receive little benefit or develop resistance after initially exhibiting a positive response. For example, immune checkpoint inhibitors (ICIs) have shown encouraging, albeit limited, success for the treatment of metastatic melanoma. ICIs are monoclonal antibodies developed to inhibit targets including CTLA-4, with agents such as ipilimumab (Yervoy), and PD-1, with agents including pembrolizumab (Keytruda) and nivolumab (Opdivo). These agents interact with the immune system to maintain homeostasis and prevent autoimmunity.

Alan J. Tackett, PhD, deputy director of Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences in Little Rock, is leveraging state-of-the-art technological approaches to discover why some patients respond better to ICI therapy compared with others. The long-term goal of this analysis is to determine whether druggable molecular pathways can be identified among nonresponders to ICI and therapeutics designed to increase responsiveness and potentially save lives.

FINDING ICI ROADBLOCKS IN MELANOMA

Recent efforts by our group have shown that melanoma progression is correlated with a disordered epigenetic information which governs cell growth and cell fate. When this equilibrium is mediated by posttranslational modification (PTM) of the histone proteins which compose the protein core of chromatin, it can influence cell proliferation, cell death, and cell differentiation. Researchers have long studied this dynamic condensation or decondensation of chromatin. The alteration of this equilibrium is mediated by posttranslational modification (PTM) of the histone proteins which compose the protein core of chromatin. This PTM equilibrium is enriched at the promoters of tumor suppressor genes in vivo. These findings were recapitulated in archival patient tissues.

To better understand epigenetic dysregulation in melanoma, we performed a quantitative proteomic analysis of histone PTMs in melanoma cell culture as well as patient tumors. We found that histone H3 at lysine 27 (H3K27me3) levels positively correlate with epithelial-mesenchymal transition (EMT) and aggressiveness in melanoma cell lines and in patient melanoma tumors. Additionally, transcriptionally repressive PTM is enriched at the promoters of tumor suppressor genes in metastatic melanoma relative to primary tumors and melanocytes. Moreover, inhibition of H3K27 methyltransferase EZH2 (EZH2i) reduces H3K27 methylation, promotes epithelial morphology, reduces proliferation, suppresses invasion, and promotes transcription and expression of tumor suppressor genes in vivo. These findings were recapitulated in archival patient tissues.

To link these patterns of epigenetic program malfunction to ICI response, we performed a quantitative proteomic analysis on treatment-naïve metastatic melanoma tumors. Results from our analysis showed that tumors that are nonresponsive to ICI therapy are characterized by elevated H3K27me3 and decreased E-cadherin expression.

Further proteomic profiling between responding and nonresponding tumors revealed differences which centered on mesenchymal transition as judged by decreased E-cadherin and other protein and epigenetic features in nonresponding tumors. In particular, E-cadherin transcript and protein levels strongly correlate with survival outcomes in patients treated with checkpoint inhibitors. These data provide supporting evidence for combining EZH2i with ICI therapy to improve responsiveness in patients with metastatic melanoma.

Our results revealed for the first time that aggressive melanoma tumor cells depend on elevated H3K27me3 levels, and that this altered epigenetic program may be associated with resistance to ICI therapy. However, it is recognized that T cells depend on EZH2 activity during tumor infiltration, evidence which contradicts the use of EZH2i in combination with ICI therapy. We found that EZH2 inhibition induces T-cell exhaustion and dysfunction in the melanoma tumor microenvironment.

FIGURE. EZH2 Protects Tumor-Infiltrating Lymphocytes from Metabolic Dysfunction

To assess the role of EZH2 in tumor metabolism, our group performed proteomic analysis of EZH2 expression in primary melanoma tumors. Results showed that EZH2 expression is associated with enhanced glycolysis and mitochondrial respiration, suggesting that EZH2 protects tumor infiltrating lymphocytes from metabolic dysfunction associated with tumor growth.

In conclusion, our findings support the potential of EZH2 inhibition as a novel therapeutic strategy for melanoma patients who do not respond to ICI therapy. Further studies are needed to explore the clinical significance of EZH2 expression and its role in tumor metabolism.

Partner Perspectives

ALAN J. TACKETT, PhD, is the deputy director of the Winthrop P. Rockefeller Cancer Institute at University of Arkansas for Medical Sciences (UAMS), the Schlarbaum Family Endowed Chair in Cancer Research, and a professor in the Department of Biochemistry and Molecular Biology, with secondary faculty appointments in Pathology and Pediatrics at the UAMS College of Medicine in Little Rock.

NATHAN L. AVARITT, PhD, is an assistant professor in the Department of Biochemistry and Molecular Biology at the University of Arkansas for Medical Sciences College of Medicine in Little Rock.

UAMS
Winthrop P. Rockefeller Cancer Institute

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Using a multi-omics approach, we identified mitochondrial dysfunction as a driver of EZH2-inhibition induced T-cell exhaustion. This loss of EZH2 function leads to metabolic exhaustion in CD8-positive T cells (FIGURE). We assessed whether reprogramming T cells with the gain-of-function EZH2 Y641F mutation that is not affected by EZH1 would enhance their ability to control tumor growth in vivo. Results from our analysis showed that CD8-positive T cells expressing the EZH2 Y641F mutation were superior at killing tumor cells and significantly inhibited tumor growth in vivo. These findings were consistent with EZH2 playing a protective role for tumor-infiltrating lymphocytes in the stress-inducing melanoma tumor microenvironment. Further, the findings suggest that therapeutic interventions combining ICI with EZH2 inhibition must account for the opposing effects of decreased H3K27me3 in tumor cells and immune cells infiltrating the melanoma tumor microenvironment.

Our results indicate that response to ICI therapy is highly influenced by an altered epigenetic program which promotes EMT though the silencing of tumor suppressor genes in melanoma. Although these data provide evidence that combining ICI therapy with EZH2i could overcome ICI resistance in some patients, the treatment must be fine-tuned because of T-cell reliance on EZH2 activity during activation and immune response.

In the study by Koss et al, we engineered tumor-specific T cells to express the gain-of-function EZH2 Y641F mutation. This alteration enhanced the control of tumor growth, demonstrating that these findings may also allow advancement of cellular therapies against melanoma tumors. References


UAMS Study Finds Cancer Treatment Creates Employment Difficulties for Some Rural Women

RURAL WOMEN ARE LIKELY to face significant challenges finding secure and reliable employment following cancer treatment if they did not already have a secure job at the time of their diagnosis, according to a new study led by University of Arkansas for Medical Sciences (UAMS) investigators.

The study, results of which were published in the Journal of Cancer Survivorship, analyzed facilitators and barriers to employment for rural women who survived cancer and how benefits such as paid time off and a supportive work environment can help those women retain employment during and after treatment.

According to the National Cancer Institute (NCI), there are an estimated 17 million cancer survivors in the United States. Studies show that nearly half of the cancer survivors in the country are working age (between 20 and 64 years) at the time of their diagnosis.

“Employment offers important benefits, from financial stability to improved mental health, but many cancer survivors struggle to return to work or to work full-time after cancer treatment,” Emily Hallgren, PhD, a member of the UAMS Office of Community Health and Research said. “Given the important benefits of work for individuals, families and society, it’s important to understand what keeps cancer survivors from working after cancer treatment as well as what helps them succeed in the workforce.”

Investigators interviewed women cancer survivors living in rural areas to determine benefits and challenges related to posttreatment employment.

Data showed that securely-employed participants who had full-time jobs with employment benefits such as paid time off and health insurance were more likely to retain their jobs through treatment. They also reported other informal benefits, such as flexible schedules, the ability to work from home and close relationships with coworkers and supervisors formed by a long period of employment. Participants with insecure employment histories—such as part-time or temporary work, often without employment benefits—faced significantly more challenges returning full-time to the workforce. Although some had paid sick time, they reported that it generally was not adequate enough for their treatment and recovery needs, and that other stressful job requirements made working through treatment more challenging. Other barriers to employment during and following cancer treatment included compromised immune systems, long-term treatment effects, limited job opportunities in rural areas, and stigma and discrimination.

“Some of our participants worked as babysitters or in schools, and their immune systems were at risk during and even after treatment,” Hallgren said. “Without employment protections or accommodations, they had to leave their jobs. Others said they felt discriminated against in future job interviews, like their cancer diagnosis was seen as a burden or a liability.”

Currently, the United States has 2 policies to protect employment for people diagnosed with disabling illnesses such as cancer: the Americans with Disabilities Act and the Family Medical Leave Act. However, those policies do not apply to temporary or informal workers or many small businesses, which may have a greater impact on rural survivors.

“Our findings highlight the need for robust supports for employees who are facing a serious illness, especially paid medical leave for all workers,” Hallgren said. “And if someone does lose or leave their job during cancer treatment, they should be connected with job placement services if they want to return to work.”

As advancements in cancer detection and treatment lead to greater chances of recovery, the NCI estimates that there will be more than 22 million cancer survivors in the country by 2030. More than two-thirds of cancer survivors now live 5 years or longer after diagnosis.
Cracking the Cancer Code Requires Both Quiet and Chaos

MATTHEW L. MEYERSON, MD, PHD, is constantly curious both about the world and the people around him. As one of the top cancer investigators on the planet, he has a talent for elevating younger scientists, turning obstacles into discoveries, and sensing future research opportunities.

As a freshman out of Harvard University, he spent a summer on a farm, baling hay and building a cow pen the farmer called “Harvard Yard.” He spent his senior year in Japan, studying in a lab at Kyoto University.

That genuine sense of wonder and wander started when he was a child growing up in Philadelphia, Pennsylvania. That’s when Meyerson discovered the work of famed architect R. Buckminster Fuller, inventor of the geodesic dome. Fuller was a university professor emeritus at the University of Pennsylvania for the final 10 years of his life. Before his death in 1983, Fuller wrote about how technology can transform people’s lives and emphasized the role of creativity, starting in childhood.

“It’s important to have a sense of wonder and to look at things and say, ‘You know, there’s always a limit to our knowledge,’” Meyerson said, who was named the second most influential scientist in the world in all fields of science by Thomson Reuters in 2014. “There are a lot of things we think are true,” he said. “And even though there’s a lot of evidence that they’re true, [the truth] ends up being different.”

UNRAVELING CANCER’S MOLECULAR SECRETS
Meyerson received his MD in 1993 and PhD in 1994 from Harvard University. Prior to joining Dana-Farber Cancer Institute in 1998, he completed a residency in clinical pathology at Massachusetts General Hospital in Boston and a research fellowship with the legendary Robert Weinberg, PhD, at Whitehead Institute in Cambridge, Massachusetts. In the early 1980s, Weinberg discovered the first human cancer-causing gene, the RAS oncogene. By 1986, he and his team also had isolated the first known tumor-suppressor gene, the retinoblastoma gene. And in 1997, Meyerson and Christopher M. Counter, PhD, identified the telomerase catalytic subunit gene.

From 2006 through 2015, Meyerson was a principal investigator for The Cancer Genome Atlas (TCGA), a landmark program aimed at
comprehensive cancer genome characterization. TCGA was a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute and was based at the Broad Institute of Massachusetts Institute of Technology and Harvard. He served as cochair of the lung cancer disease working group, and his projects have identified many mutated genes in lung cancer.

He says his work on lung cancer mutations in the EGFR gene has been his most impactful discovery to date. EGFR mutations occur mostly in nonsmokers who develop lung cancer, helping investigators understand why the disease develops in what should be a low-risk population. Like many discoveries, Meyerson says it kind of happened by good fortune. In 2003, he was working with fellow Harvard investigators William Sellers, MD, and Bruce E. Johnson, MD, trying to identify mutations in lung cancer that could be targeted therapeutically.

They had lung cancer samples from a group of Japanese patients, including women who had lung cancer but weren’t smokers. It turned out half of the patients had the EGFR mutation. Further studies with Sellers, Johnson, and Pasi A. Jänne, MD, PhD, (the 2021 Giants of Cancer Care® award winner in the lung category) showed that those with the mutation responded well to therapy.

“There was already a drug out there—gefitinib [Iressa], an EGFR inhibitor—but we didn’t know which patients it worked on or why it worked,” Meyerson said. “The study answered the question and helped us target therapy.

“It led to much improved EGFR inhibitors, and it led to this whole wave of discovery in lung cancer. There are now literally dozens of targeted inhibitors that are in use for lung cancer, and [there are] more coming all the time. It was just a huge impact on the field,” he said.

Research in lung cancer has expanded since Meyerson first started in the field in the late 1990s. He says he was frustrated by the stigma of the disease and the limited number of treatments available. Now, because more patients survive, there’s more support for research. “The individuals who really push for research in the field are the survivors. They know about the disease, they know how bad it is, and they’re still here,” he said.

Although most of Meyerson’s research has been in lung cancer, his lab has also studied microbes that cause human cancer. Comparing the genomes from 9 colon tumors with normal colon tissue from the same patient in 2011 led to a major discovery: Investigators found that colorectal cancer tissue contains high levels of several types of bacteria, most notably Fusobacterium nucleatum. Meyerson and colleagues are trying to understand whether these bacteria cause colon cancer as part of the NCI/Cancer Research UK’s Cancer Grand Challenges.

THE LAB IS A SOCIAL PLACE

Meyerson started working in a laboratory while still in high school and says he thought doing research would be easier—that he’d start working on something and figure it out. Instead, he learned that doing scientific research is like constructing a skyscraper.

“If you look at building a skyscraper, most of the time is spent digging out, structuring, and shoring up the foundation. Then when you erect the steel frame, it goes really fast,” he said. “Research is like that; you’ve got to do a huge amount of preparation before you answer a scientific question.

“You might have to build the experimental system, or if it’s a human disease, you have to collect the patient samples. Sometimes that’s weeks or months, but sometimes it’s years. Sometimes it takes many years … That balance and the need for all the prep work, that was a surprise to me.”

As a student, graduate student, and post-doctoral investigator, Meyerson learned that each lab had its own style. Some lab directors gave students a very specific project with a limited scope of responsibilities. Others gave students more independence, which also came with greater risks for the lab director. In his own lab, Meyerson gets to know students as individuals so he can best match them with projects and partners.

Rameen Beroukhim, MD, PhD, is an associate professor of medicine at Harvard Medical School, an assistant professor of medical oncology and cancer biology at Dana-Farber Cancer Institute in Boston, Massachusetts, and an attending physician at Brigham and Women’s Hospital. He joined Meyerson’s lab after he heard Meyerson give a lecture about attempts to understand the cancer genome. Beroukhim ended up working as a post-doctoral fellow with Meyerson from 2005 to 2010 and eventually opened his own lab.

“Back then, we didn’t know much about the cancer genome, but I thought, ‘Well, mutations are the essential forces that drive cancer, so understanding them would be a way of understanding cancer from the ground up,’” Beroukhim said. “At the time, he was using single nucleotide polymorphism arrays, but those arrays had been developed to genotype people to figure out [inherited alterations]—but he was applying them to cancers to understand which cancers had lost certain parts of their genomes and where those parts of the genome had been lost. That seemed like an elegant way to try to understand the genome that was different from how other people had attacked the situation.”

Beroukhim says Meyerson is unusual as a mentor because of his social skills both in and outside the lab. He makes a lot of effort not only to connect with his trainees but also to help them network with colleagues and promote their work. Off the top of his head, Beroukhim could name 5 of Meyerson’s former research fellows who are now faculty members at Dana-Farber, as well as others at Cornell University and Columbia University. “Matthew has a great way of seeing the future and what’s going to be interesting in the future—looking at research that will be informative and where people will be interested, not just now but in years to come,” Beroukhim said.

Meyerson says many people might be surprised by the social nature of the science field and how many ideas develop not as an independent “eureka” moment but as part of a conversation. “A lot of that scientific progress is thinking together and discovering together. Maybe that’s a piece individuals haven’t fully understood, that isn’t always fully captured,” he said.

Regarding pursuing an education or a career, Meyerson tells his students the same thing he tells his children. “It’s important to find your own way. Find what you like doing, what suits you personally.”

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2021 Giants of Cancer Care® Inductees

Nancy E. Davidson, MD
Julie Gralow, MD
Daniel G. Haller, MD
Toni K. Choueiri, MD
Robert Young, MD
Richard M. Stone, MD
Pasi A. Jänne, MD, PhD

To learn more about Giants of Cancer Care® program and the 2021 class, scan the QR code or visit bit.ly/3LSG2CL.
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 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-hypertension 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-MTC),* and advanced or metastatic RET-mutant MTC:1

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<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
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<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
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<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
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<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 17.5 months</strong></td>
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<td>(95% CI: 12, NE)</td>
<td>(95% CI: 12, NE)</td>
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<tr>
<td>median follow-up: 7.4 months&lt;sup&gt;1&lt;/sup&gt;</td>
<td>median follow-up: 12.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
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<th>Systemic therapy naïve (n=8)</th>
<th>Previously treated (n=19)</th>
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<tr>
<td><strong>100% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>79% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>(95% CI: 61, 100)</td>
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<td>12.5% CR + 88% PR</td>
<td>5.3% CR + 74% PR</td>
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<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 18.4 months</strong></td>
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<td>(95% CI: NE, NE)</td>
<td>(95% CI: NE, NE)</td>
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<td>median follow-up: 8.8 months&lt;sup&gt;1&lt;/sup&gt;</td>
<td>median follow-up: 17.5 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
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</table>

**Find RET. Find results on Retevmo.com.**

**Trial Design** The phase II/III, multicohort, open-label, single-arm, multicenter LIBRETTO-001 trial evaluated the efficacy of Retevmo in a population of 702 patients with metastatic RET fusion-positive NSCLC (n=332),<sup>2</sup> advanced or metastatic RET fusion-positive thyroid cancer (non-MTC)<sup>1</sup> (n=58), advanced or metastatic RET-mutant MTC (n=306), and certain other advanced solid tumors with RET alterations (n=26).<sup>2</sup> The study enrolled the following cohorts: systemic therapy-naïve patients (n=39) and previously treated (n=105<sup>11</sup>) patients who had advanced or metastatic RET fusion-positive NSCLC, systemic therapy-naïve (n=8<sup>11</sup>) and previously treated (n=19<sup>11</sup>) patients with advanced or metastatic RET fusion-positive thyroid cancer (non-MTC), and treatment-naïve (n=88) and previously treated (n=55<sup>11</sup>) 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.<sup>1,4,58</sup> ORR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v4.1,<sup>1,1</sup> 3 All results reviewed by an IRC.<sup>1,1</sup>

**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, diarhea, 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. Fatal adverse reactions occurred in 3% of patients; fatal 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 (0.40%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).
- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarhea, 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

**Metastatic RET Fusion-Positive NSCLC**

**Cobezatantin/vandetanib**

<table>
<thead>
<tr>
<th>Treatment naive (n=88)</th>
<th>Previously treated with cobezatantin and/or vandetanib (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>69% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>73% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 55, 81)</td>
<td>(95% CI: 62, 82)</td>
</tr>
<tr>
<td>9% CR + 60% PR</td>
<td>11% CR + 61% PR</td>
</tr>
<tr>
<td><strong>Median DoR was 22.0 months</strong></td>
<td><strong>Median DoR was 17.8 months</strong></td>
</tr>
<tr>
<td>(95% CI: NE, NE)</td>
<td>(95% CI: NE, NE)</td>
</tr>
<tr>
<td>median follow-up: 17.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>median follow-up: 14.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Advanced or Metastatic RET-Mutant MTC**

**Previously treated with cabozantinib and/or vandetanib**

**Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases**

**CNS DoR was ≥6 months in all responders with measurable brain metastases**

No patients received radiation therapy to the brain within 2 months prior to study entry.
Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF 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 bradyarrhythmias, 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 hypokalemia, hypomagnesemia and hypocalcemia 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. Gastrointestinal 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, withdraw 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 exposure equivalent to those 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 contraceptive 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 (1.8%), prolongation of QT interval (0.7%), diarrhea (0.7%), dyspnea (0.3%), fatigue (0.2%), abdominal pain (0.1%), hemorrhage (0.1%), headache (0.1%), rash (0.7%), constipation (0.62%), nausea (0.62%), 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.

FATAL adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades; Grade 3–4): Retevmo may cause increases in transaminases and decreases in calcium, magnesium, potassium, phosphorus, and uric acid. Adverse reactions requiring dosage reductions in >2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation. Retevmo increases acid-reducing agents and moderate CYP3A inducers. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Permanent discontinuation of RETEVMO based on the severity.

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, withdraw 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 exposure equivalent to those 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 contraceptive 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 (1.8%), prolongation of QT interval (0.7%), diarrhea (0.7%), dyspnea (0.3%), fatigue (0.2%), abdominal pain (0.1%), hemorrhage (0.1%), headache (0.1%), rash (0.7%), constipation (0.62%), nausea (0.62%), 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 are 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
Hypersensitivity
Serious hepatic adverse reactions occurred in 2.8% of patients treated with RETevmo. Increased AST occurred in 0.7% of patients, including Grade 3 or 4 events in 1.8% and increased ALT occurred in 4.9% of patients, including Grade 3 or 4 events in 0.1%.

Adverse reactions requiring discontinuation in >2% 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.

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 during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Avoid pregnancy with 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.

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

RETevmo Gene Fusion or Gene Mutation-Positive Solid Tumors
The pooled safety population described in the WARNINGS and PRECAUTIONS below reflects exposure to RETevmo as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001. Among 702 patients who received RETevmo, 65% were exposed for 6 months or longer and 34% were exposed for greater than one year. Among these patients, 50% received at least one dose of RETevmo at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years). 0.3% were pediatric patients 12 to 16 years at age; 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (47%), MTC (34%), and non-medullary thyroid carcinoma (9%).

Serious adverse reactions occurred in 33% of patients who received RETevmo. The most frequent serious adverse reaction (n ≥2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients: fatal 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 included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

Dose interruptions due to an adverse reaction occurred in 42% of patients who received RETevmo. Adverse reactions requiring dosage interruption in >2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrimidine, 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.

The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased aspartate aminotransferase (43%), increased alanine aminotransferase (ALT), increased glucose; decreased leukocytes, decreased albumin, decreased calcium, dry mouth, dizziness, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

Table 1 summarizes the adverse reactions in LIBRETTO-001.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETevmo (n=702)</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>39</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

RETEVMO™ (selpercatinib) capsules, for oral use
SE HCP BS 08MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use
SE HCP BS 03MAY2020
Clinical adverse reactions in ≤15% of patients who received RETEVMO include:

- Cough: Includes cough, productive cough
- Headache: Includes headache, sinus headache, tension headache
- Rash: Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform
- Fatigue: Includes fatigue, asthenia, malaise
- Decreased platelets: 33, 2.7%
- Increased potassium: 24, 1.2%
- Increased total cholesterol: 31, 0.1%
- Increased alkaline phosphatase: 36, 2.3%
- Increased creatinine: 37, 1.0%
- Decreased calcium: 41, 3.8%
- Increased AST: 51, 8%
- Increased ALT: 45, 9%
- Decreased albumin: 42, 0.7%
- Decreased sodium: 22, 7%
- Decreased magnesium: 24, 0.6%
- Increased potassium: 24, 1.2%
- Increased bilirubin: 23, 2.0%
- Decreased glucose: 22, 0.7%
- Decreased leukocytes: 43, 1.6%
- Decreased platelets: 32, 2.7%

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO</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>53</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>2.3</td>
<td></td>
</tr>
<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>7</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>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0</td>
<td></td>
</tr>
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<td>Decreased glucose</td>
<td>22</td>
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<td>43</td>
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<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>32</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

*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 10% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed. Dose adjustment is recommended if sustained increases 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 selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antisecretory agents 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 agent).

Strong and Moderate CYP3A Inhibitors

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib 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 QT interval with ECGs more frequently.

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib 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

RETIEVMO is a moderate CYP2C8 inhibitor and a weak CYP3A 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 recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval

RETIEVMO is associated with QTc interval prolongation. Monitor the QT 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, RETIEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETIEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryotoxicity 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 1% to 2%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 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 8 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 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 RETIEVMO and for 1 week after the final dose.
Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who
Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

<table>
<thead>
<tr>
<th>Grade 3-4 (%)</th>
<th>Grade 1-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>43 1.6</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22 0.7</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44 2.2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45 9</td>
</tr>
<tr>
<td>Increased AST</td>
<td>51 8</td>
</tr>
</tbody>
</table>

Chemistry

Hemorrhage 9 15 1.9
Cough 7 18 0
Skin
Dyspnea 8 16 2.3
Hemorrhage at puncture site hematoma
Hemorrhage, melena, mouth hemorrhage, occult blood positive, pelvic hematoma, periorbital hemorrhage, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival hemorrhage, intracranial, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage

Geriatric Use
Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (87 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.

Add: Only.

Additional information can be found at www.retevmo.com.
Checkpotnt Blockade Plus Chemotherapy Is Poised to Become Frontline SOC for Recurrent/Metastatic Nasopharyngeal Carcinoma

by KRISTI ROSA and BRITTANY LOVELY

DATA FROM SEVERAL PHASE 3 studies have proven the efficacy of adding checkpoint blockade to standard-of-care (SOC) chemotherapy in the frontline treatment of patients with recurrent or metastatic nasopharyngeal cancer. Most recently, the combination of tislelizumab (BGB-A317) and gemcitabine/cisplatin continued to demonstrate a greater progression-free survival (PFS) benefit compared with chemotherapy alone, according to updated data from the phase 3 RATIONALE-309 trial (NCT03924986) presented during an American Society of Clinical Oncology Plenary Series program.

Investigators noted that the improved PFS2 outcomes indicate the combination may improve outcomes of the treatment sequence for patients with nasopharyngeal cancer. “These results indicate that tislelizumab plus chemotherapy should be used in the first line to deliver the maximum clinical benefit,” lead study author Li Zhang, MD, said in a presentation of the data, adding that the regimen may become a SOC first-line therapy for patients with recurrent or metastatic nasopharyngeal cancer. Zhang is a professor at the Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in Guangzhou, China.

A humanized, anti–PD-1 IgG4 monoclonal antibody, tislelizumab was designed to minimize binding to receptors for the Fc region of IgG (FcγR) on macrophages to abrogate antibody-dependent cellular phagocytosis. The agent has been found to have activity in several cancers, including esophageal cancer, hepatocellular carcinoma, non-small cell lung cancer, urothelial carcinoma, and microsatellite instability-high/mismatch repair-deficient solid tumors.

RATIONALE-309 enrolled treatment-naïve patients with histologically or cytologically confirmed recurrent or metastatic nasopharyngeal cancer who had at least 1 measurable lesion per RECIST 1.1 criteria, an ECOG performance status of 0 or 1, and who were aged 18 to 75 years. A total of 263 participants were randomized 1:1 to receive tislelizumab at 200 mg on day 1 every 3 weeks or matching placebo. Patients in both arms were given gemcitabine at 1 mg/m² on days 1 and 8 plus cisplatin at 80 mg/m² on day 1, every 3 weeks, for 4 to 6 cycles. Stratification factors included gender (men vs women) and the presence of liver metastases (yes vs no).

Treatment was administered until progressive disease, unacceptable toxicity, death, or withdrawn consent. Patients in the investigatory arm could go on to receive single-agent tislelizumab at 200 mg every 3 weeks if a study investigator considered it to be clinically beneficial. Those in the control arm were permitted to cross over to receive tislelizumab monotherapy per investigator decision.

The primary end point of the trial was PFS per independent review committee assessment in the intention-to-treat (ITT) population, and secondary end points included OS, investigator-assessed PFS2, and safety. Biomarker analyses, such as PD-L1 expression and gene expression profiling (GEP), served as exploratory end points. All patients who underwent randomization (n = 263) provided baseline tumor tissue samples for biomarker assessment. Ninety-one percent (n = 240) of these patients were evaluable for PD-L1 expression, and 94% (n = 247) were evaluable for GEP.

The biomarker-evaluable population and the ITT population had similar baseline characteristics and efficacy outcomes, according to Zhang. The PFS improvement achieved with tislelizumab plus chemotherapy over chemotherapy alone was noted in all patients, irrespective of PD-L1 expression.

The GEP analysis, conducted by utilizing gene signatures that were representative of immune and tumor cell characteristics and had unsupervised clustering, revealed 3 gene expression clusters as potential biomarkers for efficacy: cold, medium, and hot.

“A ‘hot’ tumor immune profile was characterized by the highest expression of immune cells, including dendritic cells, and was associated with a greater PFS benefit vs [a] ‘cold’ tumor [immune profile] for tislelizumab plus chemotherapy,” Zhang explained.

Moreover, the PFS benefit achieved with the tislelizumab combination was noted to be highest among those with an activated dendritic cell signature. “We further investigated the individual genes that composed the dendritic cell signature and found LAMP3, a dendritic cell activation marker that was associated with PFS benefit,” Zhang added. “These results advocated...
the use of dendritic cell signature as a potential biomarker tool.”

The toxicity profile observed with tislelizumab plus chemotherapy was noted to be consistent with what had been reported at the time of the interim analysis. “The safety profile [of the combination] was manageable…no new safety signals were identified,” Zhang noted.

The most common treatment-related adverse effects (≥20%) reported with the tislelizumab combination included decreased white blood cell count, anemia, decreased neutrophil count, neutropenia, decreased platelet count, and leukopenia.

RESHAPING THE TREATMENT LANDSCAPE

In the context of checkpoint blockade in nasopharyngeal carcinoma, the results of RATIONALE-309 support earlier findings of the role immunotherapy may play for patients in the first line, according to Robert Haddad, MD, who spoke on the results in a discussion following the data presentation. Haddad is the chief, Division of Head and Neck Oncology, and McGraw Chair in Head and Neck Oncology at Dana-Farber Cancer Institute and a professor of medicine at Harvard Medical School in Boston, Massachusetts.

“If you reserve immunotherapy for the second line vs [starting it in the] first line, does that make a difference? Based on the RATIONALE-309 study, it might actually be beneficial if you start patients on immunotherapy as part of their first-line treatment early in the disease course,” Haddad said.

During the discussion Haddad contextualized the results in comparison with outcomes seen with other immunotherapeutic agents combined with chemotherapy in the first line including toripalimab plus gemcitabine and cisplatin in the phase 3 JUPITER-02 trial (NCT03581786) and camrelizumab to gemcitabine and cisplatin in the phase 3 CAPTAIN-1st trial (NCT03707509). Data from JUPITER-02 showed that treatment with toripalimab reduced the risk of disease progression by 48% compared with chemotherapy alone. The median PFS was 11.7 months (95% CI, 11.0-19.6) among the 146 patients in the investigational arm vs 8.0 months (95% CI, 7.0-9.9) among the 143 patients in the placebo arm. 4

Although the studies were not powered for OS analysis, Haddad said, “We are seeing a trend in improvement in favor of the checkpoint inhibitor added to gemcitabine and cisplatin…really a robust result [and] it would be potentially helpful to combine these studies and [perform] a meta-analysis of the data for OS but these studies were not powered for OS and those results are not mature yet.”

Haddad said common themes between these studies included that they were similar in size, had similar hazard ratios for PFS, and that although the OS data were not mature they were trending in favor of adding checkpoint blockade to chemotherapy (TABLE 1-3,4). “Crossover

with the combination vs 6.9 months (95% CI, 5.9-7.9) with chemotherapy alone (HR, 0.51; 95% CI, 0.37-0.69; one-sided P < .0001). The 12-month and 18-month PFS rates were 45.8% and 34.8%, respectively, in the investigational arm compared with 20.5% and 12.7%, respectively, in the placebo arm. 4

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which could potentially impact the OS,” Haddad said. “But, [similar to] what we saw in the RATIONAL-309 [results], despite that crossover we still saw a trend of improving OS with the triplet compared with the doublet.”

In terms of stratification based on PD-L1 expression, Haddad said it is important to note that the benefit with checkpoint inhibitors seems to be independent of PD-L1 status. “[This is] a signal we have seen repeatedly in studies where chemotherapy is combined with a checkpoint inhibitor; PD-L1 positivity seems to not matter as much in those types of studies [and] toxicity seems manageable,” he said.

UNANSWERED QUESTIONS IN METASTATIC NASOPHARYNGEAL CANCER

Haddad added that there are unanswered questions remaining for the incorporation of triplet therapy for patients with metastatic disease, including for those with nonkeratinizing disease and undetectable or low Epstein-Barr virus (EBV) viral loads.

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“[In] these studies [most] patients had nonkeratinizing nasopharyngeal carcinoma and tended to have EBV-related disease,” Haddad said. Among the patients in RATIONALE-309, 6.9% had keratinized disease and 19.8% had EBV levels below 500 IU/mL; in JUPITER-02, 1 patient had keratinizing squamous cell carcinoma and 37% of patients had a serum EBV copy number below 2000 IU/mL at baseline. Similarly, in CAPTAIN-1st, only 1 patient had keratinizing disease and 25% of patients had EBV-negative disease.

“Whether that benefit would translate to the [patients with] keratinizing carcinomas [and] non-EBV-related [disease], which we sometimes see in the Western world, remains to be determined but I have no reason to think it would not be beneficial also for those patients,” Haddad said.

In terms of the implications for these results in US-based practice, Haddad and Zhang highlighted that all 3 trials were conducted in China, where the incidence of nasopharyngeal carcinoma is much higher than in the US. However, the National Comprehensive Cancer Network (NCCN) has taken the results observed in these trials under advisement in a recent update to the head and neck cancer guidelines.3

“We had something unusual happen this year, based on the results of [the CAPTAIN-1st and JUPITER-02] studies; the NCCN adopted this combination of chemotherapy with a checkpoint inhibitor as an option for patients who have recurrent or metastatic disease,” Haddad said, pointing out that because camrelizumab and toripalimab are not available in the US, the NCCN recommends oncologists consider pembrolizumab (Keytruda) or nivolumab (Opdivo) in combination with gemcitabine/cisplatin for these patients. The NCCN still recommends gemcitabine/cisplatin alone as the preferred regimen in the first-line setting pending further information.3

Other questions Haddad noted were determining the optimal treatment duration as well as addressing sequencing questions. “[Do we give these agents for] 1 year, 2 years, or more? When you are dealing with metastatic cancer, is the checkpoint inhibitor important with gemcitabine/cisplatin when you start treatment? There was a separation of the [PFS] curves after 6 months when you compared [the combination] with placebo; is it then important to give the [checkpoint inhibitor] early on with gemcitabine/cisplatin or is it better to give it later after gemcitabine/cisplatin? Unfortunately, I don’t think we have the answer right now based on these trials, but what we know right now is that these studies are telling us if you combine these 3 drugs early [then] you have a significant improvement in PFS.”

REFERENCES
Hotspot ESR1 Mutations Drive Tumor Stickiness in Metastatic Endocrine-Resistant Breast Cancer

by BRITTANY LOVELY

THE PREVALENCE OF ESR1 MUTATIONS in endocrine-resistant metastatic breast cancer has paved an avenue for investigators to explore their role in the promotion of metastasis. ESR1 mutations have been reported in 20% to 40% of patients who received endocrine therapy with aromatase inhibitors (AIs), particularly in those who received therapy in the metastatic setting.1,2

Recent efforts have unpacked the role of somatic mutations to trigger metastatic phenotypes pulling 2 distinct hotspot mutations into focus—Y537S and D538G. Two articles recently published in Cancer Research and Nature Communications respectively unpack the previously unexplored role of ESR1 in metastatic disease progression and the association of these mutations with immune activation.3,4

“Our study provides a resource for other groups to mine the data from the cell line, from the mouse models, and from tumors,” said lead study author Steffi Oesterreich, PhD, in an interview with OncologyLive®. “Others can get access to the data, see [whether] they find something, and use the ideas for that. [It is] always very important to have it as a resource for other groups interested in an ESR1-mutant and endocrine-resistant tumors.” For more from Oesterreich, see the SIDEAR.

Early efforts to model ESR1-mutant disease in with endocrine resistance resulted in the conclusion that ESR1 mutants had context- and mutation-specific features.5 The team of investigators used the foundational insights from examining Y537S and D538G to further classify gain-of-function metastatic characteristics that may be triggered by somatic ESR1 mutations.3,5

PREVALENCE OF HOTSPOT MUTATIONS

Investigators began with an analysis of the broad genomic events observed across cohorts of patients with metastatic breast cancer to identify commonalities among patients with ESR1-mutant disease. Frequency of ESR1 mutations were compared between distant metastases and locally recurrent tumors in 2 analyses. The first analysis included compiled data from 4 cohorts of previously reported studies, which showed that among 877 distant metastases, 18% harbored ESR1 mutations, and among 44 local recurrences, no tumor samples had ESR1 mutations.2 An additional 75 recurrent tumor samples from the Women’s Cancer Research Center and the Charité Hospital in Berlin, Germany, were assessed for ESR1 mutation status using droplet digital polymerase chain reaction analysis targeting Y537S and D538G hotspot mutations. Similar to the observations of the compiled studies, mutations were identified in 25% of the distant metastases and in none of the local recurrences.2

**TABLE.** Ongoing Clinical Trials in ESR1-Mutant Breast Cancer

<table>
<thead>
<tr>
<th>Trial name/ Clinicaltrials.gov identifier</th>
<th>Intervention</th>
<th>Setting*</th>
<th>Phase</th>
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<tr>
<td>PADA-1/ NCT03079011*</td>
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<td>Frontline</td>
<td>3</td>
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<tr>
<td>SERENA-6/ NCT04964934</td>
<td>Continuing AI (letrozole or anastrozole) + CDK4/6 inhibitor (palbociclib or abemaciclib) vs switching to camizestrant + CDK4/6 inhibitor upon detection of ESR1 mutation</td>
<td>Frontline</td>
<td>3</td>
</tr>
<tr>
<td>INTERACT/ NCT04256941</td>
<td>Continuing CDK4/6 inhibitor (ribociclib, palbociclib, or abemaciclib) + AI (letrozole or anastrozole) vs switching to CDK4/6 inhibitor + fulvestrant upon detection of ESR1 mutation</td>
<td>Frontline</td>
<td>2</td>
</tr>
<tr>
<td>ELAINE-2/ NCT04432454*</td>
<td>Lasofoxifene + abemaciclib</td>
<td>Progression on endocrine therapy</td>
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</tr>
<tr>
<td>ELAINE/ NCT03781063*</td>
<td>Lasofoxifene vs fulvestrant</td>
<td>Progression on AI + CDK4/6 inhibitor</td>
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<tr>
<td>Pembro/ NCT03879174</td>
<td>Pembrolizumab + tamoxifen</td>
<td>Progression on AI</td>
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</table>

Evaluating treatments in patients with ESR1 mutations

<table>
<thead>
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<th>Intervention</th>
<th>Setting*</th>
<th>Phase</th>
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</thead>
<tbody>
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<tr>
<td>acelERA Breast Cancer/ NCT04576455*</td>
<td>Giredestrant vs physician’s choice of fulvestrant or AI</td>
<td>Progression after 1-2 lines of systemic therapy (≥ 1 targeted therapy)</td>
<td>2</td>
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<tr>
<td>AMEBRA-3/ NCT04059484</td>
<td>Amcenestrant vs physician’s choice of AI, fulvestrant, or tamoxifen</td>
<td>Progression on endocrine therapy</td>
<td>2</td>
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<tr>
<td>NCT03250676</td>
<td>H3B-6545</td>
<td>Progression on up to 1 prior chemotherapy in the metastatic setting</td>
<td>1/2</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; ET, endocrine therapy.

*All trials are designed for patients with locally advanced or metastatic estrogen receptor-positive, HER2-negative breast cancer.

*Trial is active but not currently recruiting patients.

*Not yet recruiting.
In this analysis, investigators also noted that ESR1 mutations were more prevalent among those who had received more prior lines of therapy compared with those who had wild-type disease. Further, in a meta-analysis of all samples, Y537S and D538G variant mutations were reported in 37% and 24% of tumors, respectively.1

**TUMOR CELL ‘STICKINESS’**
Following confirmation of the prevalence of ESR1 mutations in metastatic tumors, investigators evaluated mutant cell models to unpack the mechanistic behaviors of cells. Investigators looked to cell-cell interaction as a driver of metastases and observed that ESR1-mutant cell lines had a prevalence of mutant cells agglomerating together in clusters of 5 or more cells.3 Based on these findings, circulating tumor cell (CTC) clusters were examined for gene signatures in ESR1-mutant tumors. Compact cell clustering and faster aggregation of cells were reported in 2 mutant cell lines—MCF7 and T47D—specifically in MCF7/Y537S, MCF7/D538G, and T47D/Y537S cells.1

“These results show that hotspot ESR1 mutations confer increased cell-cell attachment under static and fluidic conditions, and the effect size is dependent on mutation type and genetic background,” the study authors wrote.3

Investigators next sought to build a CTC cluster gene signature based on an expression analysis from patients with estrogen receptor-positive disease with at least 2 CTC clusters. When applied to a sample of 51 metastatic tumors via RNA sequencing, investigators observed correlation of higher enrichment of CTC cluster gene signatures present in ESR1-mutant metastatic tumors.3

Finally, to examine the effect of clustering of CTCs on clinical outcomes, an analysis of ESR1-mutant tumors from 151 patients with metastatic breast cancer was performed. Clusters were detectable in 14 patients, with a median number of 15.5 (interquartile range, 4-20) cells per cluster. Patients were stratified by CTCs greater than 4 per cluster (n = 10) and fewer than or equal to 4 cells per cluster (n = 4).

In terms of prognosis, patients with stage IV indolent disease who had more than 4 clustered CTCs had worse prognosis compared with those who had fewer than 4 clustered CTCs in both the overall population (P<.0001) and in the estrogen receptor-positive/HER2-negative subgroup (P<.00001).3

In addition to the clustering CTCs, investigators noted that gap junction and desmosome genes are also more prevalent in ESR1-mutant cell lines, providing another avenue for targeted therapies. The activation of the Wnt pathway also plays a crucial role in the promotion of the migration of select hotspot mutated cells.3

**SIDEBAR.**

**ESR1 Mutations Provide Window Into Breast Cancer Metastasis**

*by KYLE DOHERTY*

**PRESENT IN APPROXIMATELY TWO-THIRDS** of estrogen receptor (ER)-positive breast cancers, the role of ESR1 mutations in disease metastasis is poorly defined.2 “It is an important research area because it is so prevalent and we [must] identify drugs we can [use] to target these ESR1-mutant [tumors],” said Steffi Oesterreich, PhD. “There is some evidence now, from some trials, such as the SOPHIA trial [NCT02492711], that some specific hormone therapy might still have some efficacy, in contrast with aromatase inhibitors, for example.” [Arriving at] the therapy [regimen] where we combine novel [agents] with drugs targeting some of these metastatic phenotypes, that is the goal. That is where we would like to get.”

In an interview with OncologyLive®, Oesterreich, a professor in the Department of Pharmacology and Chemical Biology at the University of Pittsburgh Medical Center (UPMC), coleader of the Cancer Biology Program at UPMC Hillman Cancer Center, and codirector and director of education at the Women’s Cancer Research Center, Magee-Womens Research Institute in Pennsylvania, discussed the findings of an analysis she coauthored, which examined the role of ESR1 mutations in the development of metastatic phenotypes in patients with breast cancer.

**Can you walk us through the methods used in this study?**
We used [a few] different approaches, starting with models in the lab. We used genome engineering, where we take a mutation, put it into the endogenous genome of breast cancer cell lines, then look at how these cells behave. We also use clinical specimens from patients with ER-positive, metastatic disease. We compare the tumors, which have wild-type ER with [samples] from patients where the ER is mutant. It is a large collaboration. [The authors of] these papers include cancer biologists, pathologists, surgeons, medical oncologists, [and more]. It is a very large multidisciplinary study, using approaches from different expertise.

**Please highlight some of the key findings of your research.**
Was anything particularly surprising to you?
Over the past few years, it has been shown that these ER mutations cause drug resistance, they cause resistance to hormonal therapy. We [observed this] as soon as after the mutation and local recurrences in the breast [happened]—when the tumor becomes resistant to hormonal therapy—and we compared this with the current of the mutations in distant metastases. The difference is, in 1 case, the tumor metastasized and in the other, it did not.
showed that ESR1 tumors have elevated expression of basal cytokeratins, a result not observed in wild-type tumors. This increased expression is associated with activation in pathways, including S100A8/S100A9-TLR4, representing potential blockade targets for future investigation.

As the intricacies of ESR1 come into the spotlight, results from ongoing efforts to monitor and address resistance in patients with estrogen receptor-positive/HER2-negative breast cancer will be pivotal for personalized targeted treatment strategies. Efforts to address this are underway in the prevention of localized progression (TABLE).

For example, CDK4/6 inhibitors, such as palbociclib (Ibrance), have proven effective for acquired resistance in metastatic breast cancer. Results from PADA-1 (NCT03079011) have laid the groundwork for tracing ESR1 mutations in circulating tumor DNA over the course of hormonal therapy with an AI and palbociclib. When ESR1 mutations were detected, those who switched to fulvestrant in combination with palbociclib experienced a progression-free survival (PFS) that was nearly doubled compared with those who maintained treatment with the hormonal therapy following detection.6

Rising mutations were detected prior to or concurrently with disease progression when assessed every 2 months using plasma analysis. Among a total of 1017 patients, 172 had detectable rising ESR1 mutations. These patients were randomly assigned to continue AI plus palbociclib (n = 84) or to crossover to fulvestrant plus palbociclib (n = 88). After a median follow-up of 26 months, median PFS was 11.9 months (95% CI, 9.1-13.6) for those who crossed over to fulvestrant vs 5.7 months (95% CI, 3.9-7.5) for those who did not (HR, 0.63; 95% CI, 0.45-0.88; P = .007).6

Novel strategies are also under investigation using this approach including using a novel oral selective estrogen receptor downregulator in place of an aromatase inhibitor in the phase 3 SERENA-6 trial (NCT04964934).

Both [tumors] are endocrine resistant and both are drug resistant, but 1 metastasized and the other remained in the breast.

We did not find mutations in the endocrine-resistant tumor in the breast, but we found mutations in the metastatic sites in the bone, liver, and brain. This suggests mutations play a role not only in resistance to therapy, but they [also] make the tumor metastasize. That was unexpected.

[We found] several phenotypes. You could almost say the ER is a master regulator of several metastatic phenotypes. One [we found] particularly interesting made the tumor cells stick together. Usually, you think of the tumor as becoming more metastatic when they become small individual tumor cells and they can move better. But we found that, [in this particular phenotype], the cells stick together better.

We then collaborated with other investigators to look at whether that potentially results in circulating tumor cell clusters. In the blood of patients with metastatic disease, there are tumor cells floating around and we can measure them. In patients with wild-type or ESR1-mutant tumors, we looked at whether there are more single tumor cells floating around or more clusters. In patients with ESR1-mutant disease, we found more circulating tumor cell clusters, again suggesting they stick more together.

The other very important and somewhat surprising finding was that the different mutations—although very close and localized in the ER genes—they have quite different phenotypes. Depending on the mutation, the phenotype is different. That is very important for clinical trial design. If you notice drugs targeting some of these pathways, which are activated, you [must] look and test the drugs in patients with 1 but not the other ER mutation.

Finally, the expression of these basal phenotypes resulting in altered immune infiltration was clearly an interesting finding, as well, [with] potential clinical relevance.

**What future investigative avenues are on the horizon, considering these results?**

We would like to follow up on the ultimate question: What is the therapy for patients’ ER mutations when regular endocrine therapy does not work any longer? We would like to follow up on these pathways we identified that drive metastasis in young mutant tumors.

For example, we just talked about the stickiness [of the tumor cells], and there are some drugs—not in breast cancer but in other diseases—that can target stickiness. Maybe we could test this in additional models, [and] if this is validated, there could be clinical trial testing.

We identified [several] other [implicated] pathways. Again, [we are] thinking whether these provide opportunities for the dependencies of these tumors. [We must] make sure the tumor depends on it for survival because sometimes you have upregulation of a pathway [but] that does not mean it is a high efficacy drug target.

[Another] idea is [regarding] other immune infiltration. Can it be used? This is challenging, because the analysis of the role of the immune system needs special models—you must have the entire tumor microenvironment. That is not so easy, but that is a phenotype we are following up.

**REFERENCE**


**REFERENCES**

Combinations Gain Momentum as First-Line Treatments for Unresectable Hepatocellular Carcinoma

by CHRISTINA T. LOGUIDICE

AFTER THE APPROVAL OF sorafenib (Nexavar) in 2007 as a first-line treatment for patients with unresectable hepatocellular carcinoma (HCC),1 there was almost a decade of negative studies in this population. The past few years, however, have seen rapid evolution in the treatment of advanced or unresectable HCC, with VEGF inhibitors, immune checkpoint inhibitors (ICIs), and various combination approaches demonstrating activity in the first-line setting and beyond, resulting in FDA approvals and other exciting approaches on the horizon.

During a recent OncLive Peer Exchange®, a panel of hepatobiliary tumor experts discussed several pivotal phase 3 clinical trials examining combination approaches that have expanded or are anticipated to expand the treatment armamentarium for treatment-naïve patients with unresectable HCC. They also shared their insights on several promising emerging frontline strategies in earlier stages of clinical development.

IMBRAVE150: ATEZOLIZUMAB/BEVACIZUMAB

In May 2020, based on data from the IMbrave150 trial (NCT03434379), the FDA approved atezolizumab (Tecentriq) plus bevacizumab (Avastin) as a first-line therapy for patients with unresectable or metastatic HCC.2 “The study was positive at all levels. There was a superior overall survival [OS], a superior progression-free survival [PFS], and a superior response with the combination of atezolizumab/bevacizumab,” Anthony B. El-Khoueiry, MD, said.

IMbrave150 randomly assigned 501 patients 2:1 to receive atezolizumab/bevacizumab (n = 336) or sorafenib (n = 165).3 At a median follow-up of 15.6 months (range, 0-28.6), the median OS was 19.2 months in the atezolizumab/bevacizumab arm vs 13.4 months in the sorafenib arm (HR, 0.66; 95% CI, 0.52-0.85; descriptive P < .001). The median PFS was 6.9 months vs 4.3 months, respectively (HR, 0.65; 95% CI, 0.53-0.81; descriptive P < .001). The objective response rate was 30% with the combination vs 11% with sorafenib (TABLE 1).1

The safety-evaluable population included 329 patients in the atezolizumab/bevacizumab arm and 156 patients in the sorafenib arm. Grade 3/4 treatment-related adverse effects (TRAEs) occurred in 143 (43%) and 72 (46%) of these patients, respectively. The most common TRAEs with atezolizumab/bevacizumab included proteinuria, hypertension, increased liver enzymes, and fatigue. There were 6 grade 5 bleeding events in the atezolizumab/bevacizumab arm, including 3 gastrointestinal hemorrhages, 2 esophageal varices hemorrhages, and 1 subarachnoid hemorrhage, compared with 1 bleeding event in the sorafenib arm, which was a peritoneal hemorrhage.1 “Because of the risk of bleeding with bevacizumab, this study required that patients undergo an endoscopy within 6 months prior to enrollment to ensure that if there were varices, the requirement was that they’d be treated based on institutional standard,” El-Khoueiry said.
Based on the IMbrave150 data, atezolizumab/bevacizumab has become the new standard of care for patients with unresectable HCC. “It remains standard of care for advanced-stage patients, [Barcelona clinic liver cancer] BCLC stage C, as well as some consideration in select stage B [disease],” Nicole Rich, MD, said, provided there are no contraindications to treatment, such as a history of repeated variceal bleeding.

Overall, she said the combination is well tolerated, noting few TRAEs have been observed in patients treated at her center. “The main limitation is patients’ ability to travel to get their infusion,” she said, explaining that the tyrosine kinase inhibitors (TKIs) are more convenient for many patients because they are taken orally.

Regarding patients with Child-Pugh B cirrhosis, the data on atezolizumab/bevacizumab remain unclear. Rich said atezolizumab/bevacizumab is sometimes used at her institution for “good” Child-Pugh B patients. “For example, [this would include patients with] Child-Pugh B7 in whom it may be because of albumin, not [individuals] with uncontrolled ascites,” she explained.

“The bottom line is we remain somewhat without clear guidance about whether we would be able to treat those patients safely and effectively in that setting. This has been acknowledged by the National Comprehensive Cancer Network NCCN and others, where they have specifically allocated additional guidance regarding Child-Pugh score to reflect the paucity or relative abundance of data, especially for TKIs, in that setting,” Pierre Gholam, MD, said.

**COSMIC-312: CABOZANTINIB/AZEOZILUMAB**

COSMIC-312 (NCT03755791) is a large, ongoing, global, phase 3 study that has shown significant improvement in PFS but not OS with cabozantinib (Cabometyx) plus atezolizumab (Tecentriq) compared with sorafenib in treatment-naïve patients with advanced HCC not amenable to curative treatment or locoregional therapy. The findings were reported in a virtual plenary session during the European Society for Medical Oncology (ESMO) Asia Virtual Oncology Week in November 2021.

Protocol of COSMIC-312 randomly assigns patients 2:1:1 to receive cabozantinib 40 mg orally once daily plus atezolizumab 1200 mg intravenously every 3 weeks (n = 432), sorafenib 400 mg orally twice daily (n = 217), or cabozantinib 60 mg orally once daily (n = 188). All patients must have BCLC stage B or C disease, a Child-Pugh class A score, ECOG performance status 0 or 1, and measurable disease per RECIST 1.1 criteria.

There are dual primary end points: PFS by blinded independent review for cabozantinib/atezolizumab vs sorafenib in the first 372 patients randomly assigned to these 2 arms (partial intention-to-treat [PITT] analysis) and OS for cabozantinib/atezolizumab vs sorafenib in all randomly assigned patients (intention-to-treat [ITT] analysis).

The key secondary end point is PFS for cabozantinib vs sorafenib in all randomized patients (ITT analysis).

The final PFS analysis for the PITT population showed a median PFS of 6.8 months (99% CI, 5.6-8.3) for patients who received cabozantinib/atezolizumab (n = 250) compared with 4.2 months (99% CI, 2.8-7.0) for patients who received sorafenib (n = 122). “These data are very consistent with what we saw with the combination of atezolizumab plus bevacizumab in the IMbrave150 study,” Daneng Li, MD, said.

“But what was surprising was that when investigators analyzed the data at interim analysis for OS, there was no statistical difference in terms of OS with cabozantinib at 40 mg plus atezolizumab vs sorafenib,” Li added. The median OS was 15.4 months (96% CI, 13.7-17.7) in the cabozantinib/atezolizumab arm (n = 432) and 15.5 months (96% CI, 12.1-not estimable) in the sorafenib arm (n = 217). “We’re still awaiting the mature OS data for that study, so this was interim survival. Longer follow-up is needed, but the discrepancy between PFS and OS is something to watch out for,” El-Khoueiry said. He also noted that the objective response rate for the cabozantinib/atezolizumab arm was lower than expected at 11% but that the disease control rate was high, reaching almost 80% (TABLE 2). Li speculated that the need for dose reductions of an already lower dose of cabozantinib may have contributed to the lack of OS benefit. Dose reductions because of AEs occurred in 60% of patients in the cabozantinib/atezolizumab arm vs 44% of patients in the sorafenib arm. Despite the interim analysis showing no OS benefit with cabozantinib/atezolizumab over sorafenib, El-Khoueiry said COSMIC-312 is still considered a positive study because its PFS primary end point was met. “The study was designed statistically to be positive when either end point was met,” he said.

Grade 3/4 TRAEs occurred in 2.8% of the cabozantinib/atezolizumab arm, 1.9% of the **TABLE 1. IMbrave 150 Trial Tumor Response Rates in the ITT Population**

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab/bevacizumab (n = 326)</th>
<th>Sorafenib (n = 159)</th>
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<td>ORR (95% CI)</td>
<td>30% (25%-35%)</td>
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<td>74%</td>
<td>55%</td>
</tr>
<tr>
<td>Median duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of response, months</td>
<td>18.1 (14.6-NE)</td>
<td>14.9 (4.9-17.0)</td>
</tr>
<tr>
<td>Responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with duration of</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>response ≥ 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>months</td>
<td>51</td>
<td>22</td>
</tr>
</tbody>
</table>

**CR:** complete response; **ITT:** intention to treat; **DCR:** disease control rate; **NE:** not estimable; **ORR:** objective response rate; **PR:** partial response; **SD:** stable disease.

**TABLE 2. COSMIC-312 Trial Tumor Response Rates in the ITT Population**

<table>
<thead>
<tr>
<th></th>
<th>Cabozantinib/atezolizumab (n = 432)</th>
<th>Sorafenib (n = 217)</th>
<th>Cabozantinib (n = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>11.05 (8.1%-14.0%)</td>
<td>3.7% (1.6%-7.1%)</td>
<td>6.4% (3.3%-11.0%)</td>
</tr>
<tr>
<td>CR</td>
<td>0.2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>11.0%</td>
<td>3.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td>SD</td>
<td>67%</td>
<td>61%</td>
<td>77%</td>
</tr>
<tr>
<td>DCR</td>
<td>78%</td>
<td>65%</td>
<td>84%</td>
</tr>
<tr>
<td>Median time to ORR, months (range)</td>
<td>4.0 (1.3-10.0)</td>
<td>3.5 (1.0-5.4)</td>
<td>4.2 (1.4-6.9)</td>
</tr>
<tr>
<td>Median duration of response, months (95% CI)</td>
<td>10.6 (7.1-12.7)</td>
<td>8.8 (3.0-NE)</td>
<td>15.1 (4.4-NE)</td>
</tr>
</tbody>
</table>

**CR:** complete response; **ITT:** intention to treat; **DCR:** disease control rate; **NE:** not estimable; **ORR:** objective response rate; **PR:** partial response; **SD:** stable disease.

Nicole Rich, MD

Daneng Li, MD
sorafenib arm, and 3.2% of the cabozantinib arm. Grade 5 TRAEs occurred in 1.9%, 0.5%, and 0.5% of these arms, respectively. The most common AEs with cabozantinib/atezolizumab were diarrhea, palmar-plantar erythrodysesthesia, elevated liver enzymes, decreased appetite, fatigue, and hypertension. The AEs were manageable and the safety profile was consistent with what had been previously observed for each agent.

HIMALAYA: DURVALUMAB/ TREMELIMUMAB

HIMALAYA (NCT03298451) is a large, ongoing, global, phase 3 study that recently showed a significant OS benefit with durvalumab (Imfinzi) plus tremelimumab compared with sorafenib in treatment-naïve patients with unresectable HCC.⁵ The findings were presented at the 2022 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. Unlike IMbrave150 and COSMIC-312, which combined a VEGF inhibitor with an ICI, HIMALAYA is exploring dual ICI. “This was based on earlier work in the phase 1 setting as well as a phase 2 expansion study looking at the combination of durvalumab, a PD-L1 inhibitor, plus tremelimumab, a CTLA4 inhibitor,” Li said. “Preliminary work showed an estimated response rate of 20% in this population. It was felt that this was a potential synergistic regimen that could be tested in the phase 3 setting to go up against our prior standard of care, sorafenib.”

HIMALAYA was initially designed to compare sorafenib 400 mg twice daily (control arm) with both durvalumab monotherapy, given at 1500 mg every 4 weeks, and combination therapy with tremelimumab 75 mg for a total of 4 doses followed by durvalumab 1500 mg every 4 weeks; however, recruitment to the combination therapy arm was halted after a planned analysis of the phase 2 expansion study (Study 22; NCT02519348) showed no meaningful difference between durvalumab monotherapy and the addition of tremelimumab at the 75-mg dose.

Therefore, the combination protocol was amended to use a priming dose of tremelimumab, given at 300 mg, followed by durvalumab 1500 mg every 4 weeks. The primary end point became OS for tremelimumab 300 mg/durvalumab (ie, STRIDE regimen) vs sorafenib. The key secondary end point remained OS for durvalumab vs sorafenib. Additional secondary end points included PFS, overall response rate, duration of response as assessed by the investigator per RECIST 1.1, and safety.

At the data cutoff in August 2021, the median duration of follow-up was approximately 33 months for both the tremelimumab/durvalumab and sorafenib arms. The median OS was 16.4 months and 13.8 months, respectively (HR, 0.78; 96.02% CI, 0.65-0.92; P = .0035). When examining the key secondary end point, durvalumab was superior to sorafenib, with a median OS of 16.6 months vs 13.8 months.

“Interestingly, when we looked at PFS, there was no difference with either durvalumab alone or the single dose of tremelimumab plus durvalumab vs sorafenib,” Li said. The median PFS was 3.78 months for tremelimumab/durvalumab, 3.65 months for durvalumab monotherapy, and 4.07 months for sorafenib.

“It causes some pause in the sense that it met its primary end point in terms of OS, but it didn’t meet its primary end point in terms of median PFS, highlighting that potentially not enough patients derived significant tumor control in this population to translate to that PFS,” Li said. He noted that the ORR was consistent with earlier studies (TABLE 3).³

“It will be interesting to look at the full data to see where we incorporate this regimen moving forward. It presents another option for us, given that it’s not targeting VEGF and has a completely different AE profile for our patients. But we need to take a deeper dive into the data to determine where it stands in the treatment landscape right now vs the new standard in terms of the combination of atezolizumab plus bevacizumab,” Li said.

The HIMALAYA study identified no new safety signals. Grade 3/4 TRAEs occurred in 25.8% of patients on tremelimumab/durvalumab, 12.9% of patients on durvalumab, and 36.9% of patients receiving sorafenib.

The most common grade 3/4 TRAEs in the tremelimumab/durvalumab arm included hepatic events, diarrhea/colitis, rash, pancreatic events, renal events, adrenal insufficiency, and hyperthyroid events. Grade 3/4 hepatic TRAEs occurred in 7.0% of patients on tremelimumab/durvalumab, 5.2% on durvalumab, and 4.8% on sorafenib. No TRAE of esophageal variceal hemorrhage occurred. Rates of TRAEs leading to discontinuation were 8.2% for tremelimumab/durvalumab, 4.1% for durvalumab, and 11.0% for sorafenib.

El-Khoueiry made a couple of important points regarding HIMALAYA. First, he noted that the study was not powered to compare tremelimumab/durvalumab with durvalumab monotherapy. Therefore, although durvalumab monotherapy vs sorafenib had a slightly higher OS than tremelimumab/durvalumab vs sorafenib, no conclusions can be drawn regarding how the combination may compare with durvalumab monotherapy. Second, he noted that the HIMALAYA study excluded patients with main portal vein thrombosis, whereas the IMbrave150 study did not exclude these patients.

Despite the study’s limitations, the results are still “quite impressive and intriguing,” El-Khoueiry said. “It’s very interesting that we’re at a time where we’re seeing patients with advanced HCC have a 30% OS rate at 3 years,” he added.

Tremelimumab/durvalumab was granted orphan drug designation from the FDA for the treatment of HCC in January 2020.⁶ On April 25, 2022, based on the HIMALAYA data, the FDA accepted a biologics license application for priority review, supporting the addition of a single priming dose of tremelimumab to durvalumab for treatment-naïve patients with unresectable HCC.⁷

The action date for the FDA’s regulatory decision is set for the fourth quarter of 2022.

EMERGING FRONTLINE TREATMENT STRATEGIES

Two additional major frontline studies for which the panelists are looking forward to seeing data are the LEAP trial (NCT03713593), which is comparing the safety and efficacy of lenvatinib (Lenvima) monotherapy with lenvatinib plus pembrolizumab (Keytruda),⁴ and CheckMate 9DW (NCT04039607), which is comparing the

<table>
<thead>
<tr>
<th>TABLE 3. HIMALAYA Trial Tumor Response Rates in the ITT Population⁴</th>
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<tbody>
<tr>
<td>Tumor Response</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>DCR</td>
</tr>
<tr>
<td>Median time to response, months (95% CI)</td>
</tr>
<tr>
<td>Median duration of response, months</td>
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</tbody>
</table>

CR, complete response; ITT, intention to treat; DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable disease.
safety and efficacy of nivolumab (Opdivo) plus ipilimumab (Yervoy) with sorafenib and lenvatinib monotherapies.7

In a phase 1b study (NCT03006926), lenvatinib plus pembrolizumab elicited an ORR of 36% (95% CI, 26.6%-46.2%) per RECIST 1.1 criteria.10

The median PFS was 8.6 months and the median OS was 22 months. “That’s reassuring in terms of the potency of the medication. How that will match up against lenvatinib will be interesting,” Li said. “This is the first time we’ll have a slightly different comparator arm than what we traditionally have seen so far with sorafenib.

And we know that lenvatinib tends to be a little more potent in terms of tumor control, PFS, and objective response.”

The CheckMate 9DW study has a similar design to HIMALAYA in that it is also assessing dual checkpoint inhibitors. Li noted that the nivolumab/ipilimumab combination showed promise in the phase 1/2 CheckMate 040 study (NCT01658878), with investigator-assessed ORRs exceeding 30% reported across all 3 nivolumab/ipilimumab dosing arms.11 He noted that immune-mediated toxicities will be a challenge with this regimen.

“If [LEAP and CheckMate 9DW] are also positive like the other studies we’ve seen, they will give us a wealth of choices to tailor treatments directly to our patients,” Li said.

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.
Levels of HER2 expression within the HER2-negative classification merit consideration¹

Of patients with HER2-negative tumors, ~60% have low levels of HER2 expression (IHC 1+ or IHC 2+/ISH−)¹

When standard treatment options for HER2-negative mBC are exhausted, additional therapies for varying levels of HER2 expression are needed to reshape how the story unfolds.

Daiichi Sankyo and AstraZeneca are committed to furthering the research and development of potential treatment options for women with mBC across the spectrum of HER2 expression.