Updated Results Support Repotrectinib in ROS1+ NSCLC

Updated efficacy, safety, and preliminary quality of life (QOL) findings from the TRIDENT-1 study (NCT03093116) showed that the next-generation ROS1 and TRK inhibitor, repotrectinib, has durable clinical activity in tyrosine kinase inhibitor (TKI)-naïve or TKI-pretreated patients with ROS1 fusion-positive non–small cell lung cancer (NSCLC). Results from the study were presented at the European Organisation for Research and Treatment of Cancer-National Cancer Institute-American Association for Cancer Research Molecular Targets and Cancer Therapeutics Symposium in Barcelona, Spain.1

In TKI-naïve patients, investigators reported an objective response rate (ORR) of 78.9% (95% CI, 67.6%-87.7%) and a 12-month landmark duration of response (DOR) rate of 86.1%. Patients pretreated with 1 prior ROS1 TKI and no prior chemotherapy demonstrated an ORR of 37.5% (95% CI, 24.9%-51.5%) with a 6-month landmark DOR rate of 79.5%. This activity was also observed in pretreated patients with a ROS1 G032R resistance mutation, according to investigators (ORR, 58.5%; 95% CI, 32.9%-81.6%).

In the 2-stage TRIDENT-1 trial, the phase 1 dose escalation portion determined the first cycle dose-limiting toxicities, the maximum tolerated dose, the biologically effective dose, W

Probiotic Improves Efficacy of Doublet in Metastatic RCC

When the live probiotic CBM588 was added to nivolumab (Opdivo) plus ipilimumab (Yervoy), the regimen more than doubled the response rate of the doublet in previously untreated patients with metastatic renal cell carcinoma (mRCC), according to findings from a phase 1b trial (NCT03829111). Data were presented at the 2022 International Kidney Cancer Symposium: North America.1

In patients treated with the triplet regimen (n = 19), the objective response rate (ORR) was 58% compared with 20% for those given nivolumab/ipilimumab alone (n = 10; P = .06). In the CBM588 arm, all responders achieved partial responses.
For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

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

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

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

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

Learn more at BLENREPHCP.com
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 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 14% of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at 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 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 1 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

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

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

ADVERSE REACTIONS

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

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

The most common adverse reactions (>20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (25%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

Made for this Moment
1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication is approved under accelerated approval based on response rate.

5.1 Ocular Toxicity

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

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 19% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 14%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first 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 Dose and Administration (2.3) of full Prescribing Information].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). 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 (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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

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

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

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

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

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

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

### 6.2 Immunogenicity

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

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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

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

**Data**

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

(continued on next page)
8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

- Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS

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

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia

- Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].
- Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

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

Infertility

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

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For:

GlaxoSmithKline

Research Triangle Park, NC 27709

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August 2020 BRP:1BRS

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BLMADVT190001 January 2021

Produced in USA.
I think in the decade ahead we will improve our understanding of incorporating the **right molecularly targeted agents** with the **right patients**."

— TABITHA M. COONEY, MD

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**COVER PHOTOGRAPH**

Malignant tumor in the left hemisphere of the brain.

© James Cavallini / Science Source

**PER® SPOTLIGHT**

Strategies to Refine Checkpoint Combinations Discussed at Conference
Phase 1 Trials Set Stage for Further Drug Development

Due to increasing knowledge about the genetic causes of numerous neoplasms, newer targets continue to emerge, and drug development is keeping pace.

In this issue of Targeted Therapies in Oncology®, we focus on the results of 6 phase 1 trials presented at recent conferences.

Three phase 1 trials were discussed at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium. In TRIDENT-1 (NCT03093116), repotrectinib, a next-generation ROS1 and TRK inhibitor, had durable clinical activity in tyrosine kinase inhibitor (TKI)–naive and TKI-pretreated patients with ROS1 fusion–positive non–small cell lung cancer (NSCLC; pages 26-27). Four expansion cohorts were evaluated. Patients were either TKI-naive or had some combination of prior treatment with TKIs or chemotherapy.

After a median follow-up of 18.1 months, the objective response rate (ORR) was 78.9% (95% CI, 67.6%-87.7%) in TKI-naive patients with ROS1-positive advanced NSCLC, with 4 (5.6%) complete responses (CRs) and 52 (73.2%) partial responses (PRs). In this cohort, the clinical benefit rate was 94.4% (95% CI, 86.2%-98.4%).

In another study, the HER2 tyrosine kinase inhibitor BI 1810631 demonstrated antitumor activity in patients with metastatic solid tumors with HER2 aberrations, especially in those with NSCLC who harbor HER2 tyrosine kinase domain positive mutations (pages 27-28). Investigators reported an ORR of 39% and a disease control rate of 83%. All responses, which were reported across a wide range of dosing schedules, were partial.

Clinical activity in hepatocellular carcinoma cells was observed during a phase 1/2 trial (MPSA-153-001) evaluating a novel MPS1 inhibitor, NMS-01940153E (S81694; pages 28-35). Twelve patients were evaluated in the phase 1 portion of the trial. At data cutoff, 2 patients had achieved a PR and 3 had stable disease. Duration of response was 2.6 months in 1 patient and 9.3 months in the other. Among 7 patients evaluable for α-fetoprotein, 3 experienced a decrease in levels of at least 20%.

A phase 1 trial presented at the International Kidney Cancer Symposium: North America, evaluated the addition of a probiotic to immunotherapy in previously untreated patients with metastatic renal cell carcinoma (pages 36-37). CBM588 was added to nivolumab (Opdivo) plus ipilimumab (Yervoy), which resulted in a response rate double that of the immunotherapies alone (P = .06). In the CBM588 arm, all responders achieved PRs, 21% of patients had stable disease and another 21% had progressive disease. In the nivolumab/ipilimumab arm, the 2 responders experienced a PR, 20% of patients had stable disease, and 60% experienced disease progression.

These are encouraging findings that we will continue to follow in future issues of Targeted Therapies in Oncology®.
SIGNIFICANT ATTENTION HAS been paid in recent years to the problem of physician burnout, a syndrome characterized by emotional exhaustion, depersonalization, and a reduced sense of professional accomplishment. The prevalence of burnout among physicians has reached 50%. Among oncologists, the prevalence is significant, perhaps because the long hours and challenging aspects of our work are balanced by its rewarding nature. Burnout has adverse consequences not only for doctors, but for their coworkers and patients as well. Factors that contribute to it include workplace inefficiencies, use of electronic medical records, area of specialization, payment model, and institutional and personal factors—and that was before COVID-19 added a host of new stressors.

Given that burnout has become more common and widely recognized, it is heartening to see that professional societies have taken note—and acted. The American Society of Clinical Oncology (ASCO) created a Well-Being Task Force that in 2021 released a “roadmap” to enhance oncology clinician well-being and the sustainability of oncology practices. The 2022 ASCO Annual Meeting offered a session entitled “Burnout and Mental Health in Oncology Providers: You Are Not Alone,” which I would recommend to anyone interested in the topic.

And attempts to address the problem are not limited to ASCO. I am now planning my week at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition. It’s easy to feel overwhelmed during such a gathering—from educational sessions to oral and poster presentations, from investigator meetings about ongoing trials to the get-togethers that take place at every single coffee break and the advisory meetings that start at 6 AM or end at 11 PM.

As I review the ASH agenda, I see with appreciation that the society has created ways for attendees to decompress. The Wellness Studio offers sessions entitled “Yoga,” “Money Issues Are Burning You Out,” “Fix the Way You Sit,” “A Simple Way to More Resilience,” “Financial Order of Operations,” and many others.

Clearly, ASH has recognized that the conference can be busy and stressful, and it has hired professionals to help clinicians cope and reduce burnout in the long run.

I am reminded of the advice a colleague gave me during predawn rounds early in my professional life: “Remember, your career is a marathon, not a sprint.” Those words mean more than ever to me as I enter the second half of my career. The recent death of my mother also serves to remind me that my days are numbered. It’s important for us to work hard, learn as much as we can, advance our field, and improve outcomes for patients. But we cannot forget to take care of ourselves.

John M. Burke, MD

Oncology Societies Recognize and Address Burnout During Conferences

EDITORIAL NOTE

Recognize and Address
Oncology Societies

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MIRVETUXIMAB SORAVTANSINE (ELAHERE)

NOVEMBER 14, 2022

The FDA has granted accelerated approval to mirvetuximab soravtansine (Elahere) for patients with folate receptor α (FRα)-high platinum-resistant ovarian cancer who have been previously treated with 1 to 3 prior systemic treatments, based on findings from the phase 3 SORAYA trial (NCT04296890).

In May 2022, the FDA granted priority review to a biologics license application (BLA) for mirvetuximab soravtansine in this patient population after top-line data from the phase 3 SORAYA trial that were announced in November 2021.

Mirvetuximab soravtansine is a first-in-class antibody-drug conjugate that consists of an FRα-binding antibody, cleavable linker, and the maytansinoid payload DM4, a potent tubulin-targeting agent, to kill the targeted cancer cells. SORAYA was an open-label, single arm study that evaluated the safety and efficacy of mirvetuximab soravtansine in patients with platinum-resistant high-grade serous epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer, whose tumors express a high level of FRα.

The study enrolled 106 patients who were treated with mirvetuximab soravtansine at 6 mg/kg adjusted by ideal body weight administered on day 1 of every 3-week cycle. The median number of prior lines of therapy was 3, including prior bevacizumab (Avastin) in all patients, and a prior PARP inhibitor in 48%.

Female adult patients were eligible for enrollment if they had progressed radiographically on or after their most recent line of treatment; ECOG performance status of 0 to 1; measurable disease; and adequate hematologic, liver, and kidney function.

The primary end point was objective response rate (ORR) with secondary end points including duration of response (DOR), progression-free survival, overall survival, safety, and CA-125 response. At the time of the data cutoff, the ORR with mirvetuximab soravtansine was 31.7% (95% CI, 22.9%-41.6%) among patients in the efficacy population (n = 105). The median DOR was 6.9 months (95% CI, 5.6-9.7) per investigator assessment.

The most common adverse events observed with the agent were laboratory abnormalities, vision impairment, fatigue, increased aspartate aminotransferase levels, nausea, increased alanine aminotransferase levels, keratopathy, and more.

TREMELIMUMB (IMJUDO)

NOVEMBER 10, 2022

The FDA has approved the combination of tremelimumab (Imjudo) plus durvalumab (Imfinzi) with platinum-based chemotherapy for the treatment of adult patients with metastatic non–small cell lung cancer with no sensitizing EGFR or ALK tumor alterations.

Approval was based on results from the phase 3 POSEIDON trial (NCT03164616). After 4 years of follow-up in the study, the overall survival (OS) improvement was significant.

Approximately 675 patients in POSEIDON were randomized 1:1:1 to receive tremelimumab plus durvalumab and platinum-based chemotherapy, durvalumab plus chemotherapy, or chemotherapy alone. Treatment in the triplet and doublet arms lasted 4 cycles and was administered every 4 weeks. In the chemotherapy arm, patients were treated for 6 cycles before receiving maintenance therapy.

POSEIDON evaluated progression-free survival (PFS) and OS as primary end points. Secondary end points included PFS, OS, objective response rate (ORR), and duration of response.

The median OS observed was 14.0 months (95% CI, 11.7-16.1) vs 11.7 months (95% CI, 10.5-13.1) in the chemotherapy arm (HR, 0.75; 95% CI, 0.63-0.88). At 36 months, the OS rate was 25% in the triplet arm vs 13.6% in the chemotherapy arm.

The triplet regimen also resulted in a median PFS of 6.2 months (95% CI, 5.0-6.5) vs 4.8 months (95% CI, 4.6-5.8) in the chemotherapy arm (HR, 0.72; 95% CI, 0.60-0.86; 2-sided P = .00031).

The ORR observed with the triplet was 39% (95% CI, 34%-44%) vs 24% (95% CI, 20%-29%) in the chemotherapy arm. The median durations of response were 9.5 months (95% CI, 7.2-not reached) vs 5.1 months (95% CI, 4.4-6.0), respectively.

Safety results showed that nausea, fatigue, decreased appetite, musculoskeletal pain, rash, and diarrhea were common adverse events in patients treated with the triplet. Common grade 3/4 laboratory abnormalities included neutropenia, anemia, leukopenia, lymphocytopenia, increased lipase, hyponatremia, and thrombocytopenia.

The FDA recommends a dose of 75-mg intravenous tremelimumab for patients weighing 30 kg or more plus 20-mg/kg durvalumab. In patients weighing less than 30 kg, the FDA recommends 1-mg/kg tremelimumab and 20-mg/kg durvalumab.

BRENTUXIMAB VEDOTIN (ADCETRIS)

NOVEMBER 10, 2022

The FDA has granted approval to the combination of brentuximab vedotin (Adcetris) plus doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVE-PC) in pediatric patients 2 years and older with newly diagnosed, high-risk classical Hodgkin lymphoma.

This approval is supported by findings from the phase 3 AHOD1331 trial in which the combination in this patient population. Findings revealed that adding the antibody-drug conjugate to AVE-PC significantly improved event-free survival (EFS) compared with the standard-of-care treatment AVE-PC.

The investigative arm, patients experienced a reduction in the risk of disease progression or relapse, second cancer, or death of 59% (HR, 0.41; 95% CI, 0.25-0.67; P = .0002).

The multicenter, randomized, open-label AHOD1331 trial was conducted by the Children’s Oncology Group and sponsored by the National Cancer Institute. The study is the largest to be performed in pediatric patients with newly diagnosed, high-risk Hodgkin lymphoma.

A total of 587 patients, aged 2 to 21 years, were enrolled in the trial. Enrollment in the trial was open to patients who had previously untreated Hodgkin lymphoma with stage IIB and bulky disease, stage IIB disease, stage IVa disease, or stage IVb disease.

Investigators randomly assigned patients to receive 5 cycles of either standard dose-intensive chemotherapy ABVE-PC or brentuximab vedotin plus AVE-PC every 21 days with granulocyte colony-stimulating factor support.

The primary end point of the trial was EFS with secondary end points including proportion of patients with early response and proportion of patients experiencing grade 3 or higher peripheral neuropathy. Other exploratory end points consisted of Childhood Hodgkin International Prognostic Score (CHIPPS), the dose of radiation received by normal tissues following chemotherapy on either arm, efficacy of involved site radiotherapy, risk of relapse, and pharmacokinetics.
CEMIPLIMAB-RWLC (LIBTAYO) | NOVEMBER 8, 2022

The combination of cemiplimab-rwlc (Libtayo) plus platinum-based chemotherapy was approved for the treatment of adult patients with advanced non–small cell lung cancer with no EGFR, ALK, or ROS1 aberrations, according to an FDA announcement.

Approval of cemiplimab for this indication is based on results from a randomized, multicenter, multinational, double-blind, active-controlled, phase 3 trial (Study 16113; NCT0349614). In the study, cemiplimab in combination with platinum-based chemotherapy achieved a statistically significant and clinically meaningful improvement in overall survival (OS) vs placebo plus chemotherapy (HR, 0.71; 95% CI, 0.53-0.93; 2-sided P = 0.0140). The median OS was 21.9 months (95% CI, 15.5-not evaluable) in the cemiplimab plus chemotherapy arm compared with 13.0 months (95% CI, 11.9-16.1) in the placebo plus chemotherapy arm. Cemiplimab/chemotherapy also demonstrated positive results for the secondary end points of progression-free survival (PFS) and overall response rate (ORR).

Study 16113 included 466 patients in the experimental arm who received treatment every 3 weeks for 4 cycles followed by cemiplimab and maintenance chemotherapy. Patients in the control arm were given placebo plus platinum-based chemotherapy every 3 weeks for 4 cycles followed by maintenance chemotherapy.

In terms of PFS, the median per blinded independent committee review was 8.2 months (95% CI, 6.4-9.3) in the cemiplimab/chemotherapy arm vs 5.0 months (95% CI, 4.3-6.2) in the chemotherapy arm (HR, 0.56; 95% CI, 0.44-0.70; P < 0.0001). The confirmed ORR in the cemiplimab arm was 43% (95% CI, 38%-49%) compared with 23% (95% CI, 16%-30%) in the placebo arm.

The most common adverse events were alopecia, musculoskeletal pain, nausea, fatigue, peripheral neuropathy, and poor appetite.

The FDA recommends administering cemiplimab intravenously at 350 mg every 3 weeks.

LEUPROLIDE ACETATE | NOVEMBER 2, 2022

The FDA has granted approval to an abbreviated new drug application for leuprolide acetate injection for patients with advanced prostate cancer, according to a press release from Amneal Pharmaceuticals, Inc.

This injection is indicated for palliative treatment in patients with advanced prostate cancer. The abbreviated application is used for the review and approval of generic drugs. Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone, which acts as an inhibitor of gonadotropin secretion. The injection is a sterile, aqueous, clear solution intended for subcutaneous injection.

The leuprolide acetate injection is available in a 2.8-mL multiple-dose vial containing leuprolide acetate, 5 mg/mL; sodium chloride, USP (6.3 mg/mL) for tonicity adjustment; benzyl alcohol, NF as a preservative (9 mg/mL); and water for injection, USP.

In preclinical studies following an initial stimulation, administering leuprolide acetate continuously resulted in suppression of ovarian and testicular steroidogenesis that was reversible upon the discontinuation of the drug. Leuprolide acetate has also shown the ability in preclinical studies to inhibit the growth of select hormone-dependent tumors, including prostatic tumors in a Noble and Dunning male participants, DMBA-induced mammary tumors in female participants, and atrophy of the reproductive organs.

Results from clinical trials showed that when leuprolide acetate was subcutaneously administered in single daily doses, it led to an initial increase in circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This resulted in a transient increase in gonadal steroid levels, whereas continuous and daily administration of the drug led to decreased levels of LH and FSH in patients.

In male patients, testosterone was reduced to castrate levels. For female patients who were premenopausal, estrogens were reduced to postmenopausal levels. These decreases occurred within 2 to 4 weeks following the initiation of treatment. Castrate levels of testosterone have been shown for periods of up to 5 years in patients with prostate cancer.

In a controlled study, the use of subcutaneous leuprolide acetate administered at 1 mg daily was compared with diethylstilbestrol given at 3 mg daily. After 2 years, survival rates and objective response to treatment were similar between the 2 groups.

COBIMETINIB (COTELLIC) | NOVEMBER 1, 2022

The oral MEK1/2 inhibitor cobimetinib (Cotellic) was approved by the FDA for the treatment of patients with histiocytic neoplasms, including Erdheim-Chester disease, Rosai-Dorfman disease, and Langerhans cell histiocytosis.

The basis of the approval comes from findings of a single-institution phase 2 trial (NCT02499772) conducted by Memorial Sloan Kettering Cancer Center (MSKCC) and Genentech, Inc in adult patients with histiocytic disorders.

*The approval of cobimetinib represents the collective hard work of several years of investigation by many MSK researchers. There have been tremendous advances in the field of rare cancers as a result of research and trials conducted at MSK, and this approval is an excellent example of a practice-changing outcome,* said Eli L. Diamond, MD, a neuro-oncologist and neurologist at MSKCC and principal investigator of the trial, said in a press release. "There has always been an unmet need for patients with histiocytosis, and we are thrilled that with this approval, these patients will now have access to a viable treatment option," said Diamond.

Previously, cobimetinib received FDA approval in combination with the BRAF kinase inhibitor vemurafenib (Zelboraf) for the treatment of patients with BRAF-positive melanoma, based on data from the phase 3 coBRIM study (NCT01689519).

In the phase 2 trial, patients with a histiocytic neoplasm were enrolled to determine the effects of cobimetinib in this patient population, regardless of tumor genotype. Patients with BRAF V600 mutations were eligible if they had intolerance or resistance to prior BRAF-targeted therapy or were unable to access BRAF inhibitor therapy.

Those enrolled in the study were administered cobimetinib starting at 60 mg daily for 21 days of each 28-day cycle. Investigators evaluated the primary end point of overall response rate (ORR) by fluorodeoxyglucose positron emission tomography (PET), as assessed by a radiologist, and the secondary end points of duration of response and progression-free survival by PET as well as safety and ORR by RECIST v1.1 criteria.
Overcoming Inertia to Implement Value-Based Care
By Lynn Carroll

As the health care industry increasingly shifts to value-based care (VBC) and alternative payment models, its biggest challenge is inertia. Fee for service (FFS) and pay for performance (P4P) have been entrenched for years, along with the business processes and costly legacy systems that support them.

To fully realize VBC, these existing infrastructures must be transformed. Health care organizations can be strongly resistant to change, however. A primary obstacle involves investments in internal systems. In both cases, existing infrastructure creates a commitment to the status quo that makes change difficult or even impossible.

Most health care information technology systems are structured to enable FFS and/or P4P payment models under which the exchange of data is 1 to 1. For example, a primary care physician (PCP) sees a patient, generates a claim, and submits it to the payer for payment.

A VBC ecosystem requires hierarchical and far more complex relationships among providers, payers, community-based organizations, social service networks, and other stakeholders in the VBC network. In addition to facilitating payments, a VBC platform must support social determinants of health, quality reporting, and other uses.

Legacy Limitations
Within these networks are relationships in which a PCP in one network may be engaged in other networks under various contractual arrangements with other entities. An organization that offers mental health services, for example, may have contracts with health care providers across multiple VBC arrangements. Such a “network of networks” can work only with an infrastructure that supports the hierarchies between these entities.

One major barrier to the effectiveness of a VBC network run on legacy infrastructure is providers’ inability to manage a complex multistakeholder network while accommodating the episodic requirements of payment models that are no longer claim-centric. Another common obstacle is providers’ failure to obtain timely data reporting and to accurately forecast contract performance.

In a VBC network hierarchy, sources of funding sit at the top. Risk-bearing entities—such as hospitals, accountable care organizations, independent practice associations, direct primary care, and specialty carve-out organizations—reside in the middle. Participating providers are at the bottom.

These relationships for movement of funds, data exchange, and patient episode tracking are “many to many” in nature. They enable providers to participate in VBC programs as individuals, as part of groups, across multiple locations, and across different payer programs and networks. Most legacy systems lack the flexibility and interoperability to implement and sufficiently scale such VBC programs.

Fortunately, technology exists that provides capabilities required to execute VBC programs without replacing infrastructure. A purpose-built VBC cloud-based platform with the flexibility to be implemented as Software as a Service, Platform as a Service, or Data as a Service can ease the transition from other models.

Using an incremental implementation approach, existing organizations can implement their value-based programs in a step-by-step process that provides the clear insights and quality measures needed for success.

Fear of Complexity
Another obstacle to VBC adoption is concern that managing a complex, hierarchical, many-to-many network would be overwhelming. This would be a legitimate fear if one tried to build a VBC network on top of legacy systems because these systems do not support the hierarchical relationship structures necessary to support value-based contracts. Any attempts to fit the complexity of value-based contracts into such a legacy system is not going to scale and will require manual processing and labor, making it inefficient, costly, and prone to error.

Traditional approaches and legacy systems cannot scale the orchestration of cascading payment models, under which payer-provider collaborations incorporate risk-bearing entities and downstream participating providers. This reduces providers’ ability to accelerate adoption of varied payment models.

In contrast, a cloud-based microservices platform smooths onboarding of stakeholders and includes mechanisms for financially rewarding them for their roles. These mechanisms make the administration of funding pools one of the most vital functions of value-based execution.

If stakeholders believe they need to replace existing infrastructure with another investment, VBC adoption will lag. Concerns about the complexities of VBC also hinder adoption. Cloud-based microservices platforms running on top of legacy systems can enable provider organizations to build a value-based administrative data architecture that will help them meet the VBC goals of improving patient outcomes while reducing costs. TT

Lynn Carroll is chief operating officer of HSBlox. The company makes software to assist in administering value-based care programs.

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As Cancer Screenings Start Back Up, Inequities Persist

By Conor Killmurray

WHEN THE COVID-19 pandemic forced patients with cancer to stay home and take extra precautions, it also forced thousands of others to delay routine screenings that would inform them of a potential cancer diagnosis. Results of a study conducted by the Community Oncology Alliance (COA) showed significant reductions in screenings at the beginning of the COVID-19 pandemic. Screenings in April 2020 compared with April 2019 showed breast (–85%), colon (–75%), prostate (–74%), and lung (–56%) cancer screenings all decreased.1

At the time of the study’s publication, lead study author Debra Patt, MD, PhD, MBA, FASCO, said that as cancer becomes more advanced, it becomes a ticking time bomb; the impact of these delayed screenings will be felt for years as rates of morbidity and mortality increase.

Now, a study from COA showed that in 2022 breast cancer screenings have increased from their 2020 lows, but screening disparities among White patients and patients from minority backgrounds have been exacerbated.2

In an interview with Targeted Therapies in Oncology™, Patt, executive vice president of policy and strategic initiatives at Texas Oncology and member of the COA Board of Directors, discussed the highlights of these studies and what the lasting impact of delayed cancer screenings could look like for patients. Moreover, she addressed what has been done about this issue and what still needs to be worked on.

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What are some of the highlights of the original study COA conducted?
PATT: We characterized utilization of screening, diagnostic, and treatment services for cancer in 2020 vs 2019. What we observed is that for the 6 million patients in the study, there was a substantial decrease in screens for cancer for patients with breast, colon, lung, and prostate cancer observed during 2020.

These decreases in screenings also translated into decreases in cancer-related biopsies, surgeries, and treatment. One could then estimate that the natural consequences of delays in diagnosis is that patients will present with later stages of cancer, which will increase morbidity and mortality related to those cancers.

How does that look in a real-world scenario?
[For instance,] I’m a breast cancer specialist and if we were to diagnose a patient with stage III estrogen receptor-positive breast cancer this year, it would have been stage I. If that happens, the patient would [now] require more treatment; they will have to have chemotherapy, they will have to have a more aggressive surgery, and they will have to have radiation instead of maybe just surgery. What we’re observing at this point is what we call a stage migration, where patients are diagnosed at later stages of cancer, but I think that true estimates of cancer mortality will take several years to manifest.

How have ethnic minority groups been impacted by delays in care?
For individuals who are ethnic minorities, and individuals of lower socioeconomic status, they already have barriers to appropriate health care. During the pandemic those barriers were magnified and it was more difficult for these patients to get health care.

What were some of the efforts you were a part of to address this issue?
We identified a universal hotline [for people to contact so they] would understand the availability of screening studies in various communities.

That’s important because you have states where screening is available, and generally if you have commercial insurance, then screening, like a mammography, is covered. However, there’s a lot of individuals that don’t have health insurance. I live in the state of Texas, where there are about 30 million Texans, and 5 million Texans without any health insurance, so screening becomes a problem when you must pay for it.

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SIGNIFICANT AMOUNT OF research into the treatment of brain cancers is being conducted, and with multiple strategies being evaluated simultaneously, hope for future effective treatment options is increasing.

Primary brain cancers are aggressive, resulting in low survival rates, and pose significant challenges to effective treatment.1 Therapeutic strategies include surgery, chemotherapy, and radiotherapy. Intracranial surgery carries significant inherent risk, and it is difficult to achieve adequate removal of tumor cells because of the difficulty of separating tumor tissue from normal tissue. There are many barriers to effective chemotherapeutic approaches, such as inadequate blood-brain barrier (BBB) penetration, poor drug stability, and adverse events (AEs) due to nonspecific targeting. Moreover, radiotherapy is hampered by tumor cells being inherently resistant to ionizing radiation.1 Additionally, brain tumors exhibit several characteristics conducive to treatment resistance, such as epigenetic dysregulation, genetic anomalies, cellular plasticity, immunosuppression, and metabolic adaptability.2

Because of the numerous mechanisms by which brain tumors resist therapies, many treatment avenues are currently under investigation. Tabitha M. Cooney, MD, director of the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic of the Dana-Farber Cancer Institute and assistant professor of pediatrics at Harvard Medical School, likened today’s research to that of the development of chemotherapies for childhood leukemia. “Current research is a modern-day adaptation of the mid-1900s, when childhood leukemia was completely fatal and combinations of different conventional chemotherapies were required to make a difference,” Cooney said. “At that time, that approach seemed ‘crazy.’ The current era will involve combinations across treatment types such as targeted, immune, and conventional therapies.”

Glioma

\(^{186}\)RNL is a nanoliposome containing radioactive rhenium 186 (\(^{186}\)Re) that delivers high-energy β and γ particles to a tumor and is administered by convection-enhanced delivery (CED).3 A recent phase 1/2a dose-escalation trial (ReSPECT-GBM, NCT01906385) evaluated a single administration of \(^{186}\)RNL in patients with recurrent malignant glioma. The 23 included patients who had poor prognostic indicators, a mean of 1.6 prior treatments, and a mean tumor volume of 8.1 mL, and they were spread across 8 dose cohorts receiving 1.0 mCi to 22.3 mCi in 0.6 mL to 8.8mL.3 The median overall survival (OS) in patients receiving more than 100 Gy mean absorbed radiation dose to the tumor was 22.9 months (95% CI, 8.8-42.3) compared with 5.6 months (95% CI, 1.6-9.4) for patients receiving 100 Gy or less. The median OS for the overall population was 9.4 months (95% CI, 5.8-13.2).3 A recommended phase 2 dose of 22.3 mCi/8.8 mL is recommended for gliomas less than 15 mL in volume for an upcoming phase 2b trial.

Anlotinib

Anlotinib is a tyrosine kinase inhibitor with numerous targets, including vascular endothelial growth factor receptor (VEGFR) 2, fibroblast growth factor receptor 1, and platelet-derived growth factor receptor β.4 Preclinical studies identified that the activity of anlotinib against glioblastoma cells, which was enhanced by the addition of temozolomide (Temodar).5 At the 2022 European Society for Medical Oncology (ESMO) Congress, results were presented from an open-label, single-arm, phase 2 trial of anlotinib in patients with histologically confirmed high-grade glioma who had progressed after surgery followed by radiotherapy and temozolomide (Temodal) chemotherapy (NCT04822805).2 Once-daily oral anlotinib 12 mg was administered for 14 days every 3 weeks until disease progression or unacceptable
Although few treatment options are currently available to treat patients with various primary brain tumors, primarily glioma and glioblastoma multiforme, ongoing research with various agents are providing hope and promise for new options to be approved in the years to come.

Toxicity occurred. Complete responses (CRs) were observed in 4 of 26 evaluable patients at the data cutoff date, with another 7 experiencing partial responses (PRs), for an objective response rate (ORR) of 42.3% (11/26). A disease control rate of 88.5% was observed with 12 patients presenting with stable disease (SD). The median progression-free survival (PFS) was 8.3 months (95% CI, 3.5-13.1), and the 6-month PFS rate was 64.9%. Any-grade AEs were reported in 19 patients (73.1%), and grade 3 events occurred in 6 patients (23.1%). No AEs greater than grade 3 were observed. These results reveal promising anti-tumor activity and adequate tolerability for patients with recurrent high-grade glioma. Several phase 2 studies evaluating anlotinib in glioblastoma are underway.

Dabrafenib and Trametinib
The combination of the BRAF inhibitor dabrafenib (Tafinlar) and the MEK inhibitor trametinib (Mekinist) has been developed specifically for cancers harboring BRAF V600 mutations, including low- and high-grade glioma in adults and pediatric low-grade glioma (pLGG). Results from the phase 2, open-label ROAR basket trial evaluating dabrafenib and trametinib across numerous BRAF V600E-mutated cancers in adult patients (NCT02034110) indicated clinically meaningful activity in patients with recurrent or refractory low- and high-grade glioma. The ORR among patients with high-grade glioma was 33% (15/45; 95% CI, 20%-49%), including 3 CRs and 12 PRs, at a median follow-up of 12.7 months.

Current research in targeted therapies, immunotherapies, and other new treatment modalities are offering hope for effective future treatment options for patients with brain tumors.
**Brain Tumors**

ORR of 69% (9/13; 95% CI, 39%-91%), with 1 CR, 6 PRs, and 2 minor responses was observed in patients with low-grade glioma at a median follow-up of 32.2 months. AEs of grade 3 or worse were observed in 53% (n = 31) of patients and included fatigue (9%), headache (5%), and neutropenia (5%).

Dabrafenib with trametinib has also shown efficacy in patients with pLGG, according to data recently presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. The randomized, phase 2 study included patients aged between 1 and 17 years with BRAF V600 mutation-positive gliomas treated in the first-line setting (NCT02684058). Dabrafenib plus trametinib achieved an independently assessed overall response rate of 47% (95% CI, 35%-59%) compared with 11% (95% CI, 3%-25%) in the standard-of-care carboplatin plus vincristine arm (odds ratio, 7.2; 95% CI, 2.3-22.4; P < .001). Dabrafenib plus trametinib also produced a clinical benefit rate (CBR; CR + PR + SD at ≥ 24 weeks) of 86% (95% CI, 76%-93%) and a median PFS of 20.1 months (95% CI, 12.8-not estimable) compared with a CBR of 46% (95% CI, 30%-63%) and a median PFS of 7.4 months (95% CI, 3.6-11.8) in the carboplatin plus vincristine arm (HR, 0.31; 95% CI, 0.17-0.55; P < .001). Additionally, fewer grade 3 or greater AEs were observed with dabrafenib plus trametinib (47% vs 94%, respectively) along with fewer discontinuations due to AEs (4% vs 18%). The most frequent AEs in the investigational arm were pyrexia (68%), headache (47%), and vomiting (34%).

First-line treatment of pLGG with dabrafenib and trametinib has the potential to significantly improve outcomes compared with traditional chemotherapy based on these significant results.

**DSP-0390**

Gliomas support rapid growth by upregulating cholesterol synthesis, and increased expression of genes associated with cholesterol synthesis correlates with poorer patient survival. DSP-0390 is a small-molecule inhibitor of emamipil-binding protein that selectively kills glioblastoma cells by inhibiting de novo cholesterol synthesis. In preclinical research, DSP-0390 has shown significant antitumor activity in orthotopic xenograft models of human glioblastoma. A phase 1 trial in patients with recurrent, high-grade glioma (NCT05023551) is under way in the United States and Japan. The dose-expansion phase will enroll 20 to 40 patients with measurable WHO grade IV glioblastoma that has progressed after primary therapy, who will receive once-daily oral DSP-0390.

**Tovorafenib**

Tovorafenib (DAY101) is an oral, small-molecule, type II pan-RAF inhibitor that is highly selective and able to penetrate the central nervous system. In addition to targeting the BRAF V600E mutation, tovorafenib also targets RAF gene fusions; however, unlike type I RAF inhibitors, tovorafenib does not result in activation of the MAPK pathway via RAS-dependent paradoxical activation. In a phase 1 trial (PNOC014) of tovorafenib in pediatric patients with recurrent/progressive low-grade glioma, a clinical benefit was observed in 7 of 8 patients with tumors containing RAF fusions. The drug was also well tolerated. Initial results from the ongoing, open-label, single-arm phase 2 FIREFLY trial (NCT04775485; PNOC026) of tovorafenib in pediatric patients with RAF-altered recurrent or progressive LGG appear promising, according to a news release from earlier this year. An overall response rate of 64% and CBR of 91%, with 14 PRs and 6 patients with SD, were observed in 22 patients evaluable by Response Assessment for Neuro-Oncology (RANO). Tumor shrinkage of 19% to 43% was noted in all 6 patients with SD. Both patients with BRAF fusions and the BRAF V600E mutation who had previously received MAPK-targeted therapy were among the responders, and all responders remained on therapy. A global phase 3 clinical trial (FIREFLY-2/LOGIC) is set to evaluate the efficacy and safety of tovorafenib monotherapy compared with investigator’s choice of 1 of 3 chemotherapy options in patients with newly diagnosed pLGG with an activating BRAF mutation.

Regarding progress in pLGG, Cooney said, “Pediatric oncologists now understand low-grade glioma is a chronic illness that places significant burden on patients and families and this era of RAF inhibition is very exciting and appealing. Not only are we trying to discern the short-term benefit of these agents, but also if we can achieve long-term benefits to quality of life and patient burden resulting in the ability to thrive in their normal educational and social attainments.”

Cooney believes the outlook is positive for targeted agents in general. “We’re in early phases and I think in the decade ahead we will improve our understanding of incorporating the right molecularly targeted agents with the right patients and becoming more sophisticated and assertive with potential combination strategies.”

**Glioblastoma Multiforme**

**L19TNF**

The pro-inflammatory cytokine tumor necrosis factor (TNF) has the potential to initiate an immune response against tumor cells, according to the results of the phase 1/2 GLIOMOON trial (NCT03779230), but its application has been hindered by significant AEs when dosed to achieve desired activity levels. L19TNF was developed in the hopes of specifically targeting tumor cells by fusing an antibody (L19) that binds an epitope of fibroectin specific to the extracellular matrix of tumor cells. Recently, results from a preclinical trial of L19TNF in combination with PD-1 inhibitors, the VEGF inhibitor bevacizumab (Avastin), or the chemotherapy lomustine, were presented at ESMO 2022. In 2 immunocompetent orthotopic glioma mouse models, L19TNF with lomustine resulted in the strongest increase in lymphoid cells infiltrating the tumor and robust synergistic anti-tumor activity, ultimately curing the most tumors in mice, and no drug activity was observed in immunodeficient mice. The combination of L19TNF and lomustine has entered a phase 1/2 trial (GLIOSTAR; NCT04573192) and appears to be well tolerated in the first few patients dosed. PRs (2/6) and durable SD have been observed so far, including in patients with the inherently negative prognostic indicator of an unmethylated MGMT promoter. Of the 2 patients with a PR, 1 had a 98% reduction in tumor size from baseline and the other had an 83% reduction.
We’ve entered a hopeful era, to truly reduce morbidity for highly survivable tumors that we haven’t seen before. For aggressive tumors we have hope that some of these agents will have a role to play.”

—Tabitha M. Cooney, MD

**Veliparib**
PARP is an important component of the DNA damage repair mechanism. Resistance to temozolomide is common in patients with brain tumors, and DNA damage repair is a mechanism implicated in the development of resistance. Therefore, combining temozolomide with the PARP inhibitor veliparib has the potential to counteract these mechanisms and has proved significantly beneficial in glioblastoma patient-derived xenografts with MGMT promoter hypermethylation. Unfortunately, recent results from the phase 2/3 Alliance A071102 trial (NCT02152982) assessing veliparib or placebo with adjuvant temozolomide in patients with newly diagnosed glioblastoma harboring MGMT promoter hypermethylation were unremarkable. No significant differences between the combination of temozolomide with veliparib and temozolomide with placebo were observed among the 421 patients receiving treatment, in terms of median OS (28.1 vs 24.8 months, respectively; \( P = .15 \)) or median PFS (13.2 months vs 12.1 months; \( P = .31 \)). However, the veliparib combination did result in a trend in extended survival following retreatment with temozolomide at first recurrence, with a median post-recurrence OS of 17.0 months vs 12.6 months in the placebo arm (\( P = .03 \)). Therefore, the addition of veliparib to temozolomide therapy may still benefit a subset of patients with glioblastoma; identifying which patients will benefit, though, remains a challenge.

**Atezolizumab**
Overall, immune checkpoint inhibitors (ICIs) have demonstrated little efficacy against glioblastoma. Previously published results indicated that atezolizumab (Tecentriq) in combination with temozolomide and radiation therapy provided modest efficacy in 60 patients with newly diagnosed glioblastoma and unknown MGMT methylation status. In post hoc analyses of a phase 1/2 trial (NCT03174197), investigators continued to search for markers identifying patients who benefited from the addition of atezolizumab. Unfortunately, T-cell levels and PD-L1 expression did not correlate with outcome; however, glial fibrillary acidic protein emerged as a potential negative predictive biomarker. Results of further analysis of data from this trial, in terms of baseline tumor genome and gut microbiota, were recently presented at ASCO 2022. Two sequencing methods (whole exome [WES], somatic copy number alteration [SCNA], and RNA-seq) identified EGFR aberrations as being associated with relatively worse median OS compared with patients with PTEN alteration-rich tumors, and patients with identified IDH1 mutations exhibited the longest median OS. A gene set enrichment analysis identified a group of tumor genes with roles in lymphocyte activation and immune response that was enriched in patients with longer OS (\( P < .01 \)). Distinct fecal bacterial taxa were also associated with OS (Ruminococcus spp.) and treatment response (Eubacterium spp.), warranting further investigation.

**Selinexor**
Exportin-1 (XPO1) is a nuclear export protein that readily crosses the BBB and is effective in various solid and hematologic tumors. Selinexor (Xpovio) is a selective inhibitor of XPO1 that reactivates tumor suppressor proteins and reduces translation of oncogene mRNAs. The oral medication selinexor (Xpovio) is a selective inhibitor of XPO1 that readily crosses the BBB and is effective in various solid and hematologic tumors. Selinexor was recently evaluated in 76 adults with recurrent glioblastoma and a Karnofsky performance status of 60 or greater in the phase 2 KING trial (NCT01986348), which was later terminated by the sponsor. Selinexor was administered at various doses, with patients planning to undergo cytoreductive surgery receiving up to 3 doses twice weekly (n = 8), Patients not undergoing surgery received dosages of 50 mg/m² twice weekly (n = 24), 60 mg twice weekly (n = 14), or 80 mg once weekly (n = 30). The 6-month PFS rate, the primary end point, was highest in the patients who received 80 mg once weekly (17%; 95% CI, 7.7%-38.3%), with a RANO-response rate of 10% (95% CI, 2.1%-26.5%). A single fatal AE occurred, and 26 patients (34%) across all treatment groups experienced serious AEs. An exploratory analysis found that patients with mutations in PDX1, EP400, or DOCK8 tended to survive longer than others. Ongoing clinical trials in glioblastoma are evaluating selinexor in combination with temozolomide (NCT04216329) and standard-of-care chemotherapy (NCT04421378).

**NT-17**
Radiotherapy and temozolomide therapy often result in extended systemic lymphopenia, which reduces patient survival. NT-17 (efi neptakin alfa) is a first-in-class, long-acting recombinant interleukin-7 agent that has been shown to reverse lymphopenia, increase cytotoxic CD8-positive T cells (both systemically and within the tumor), and improve survival in mice with orthotopic gliomas. In an ongoing phase 1/2 trial in patients with high-grade gliomas treated with chemoradiation (NCT03687957), NT-17 was well tolerated. Treatment resulted in increased cytotoxic T cells and natural killer cells along with rapid increases in key cytokines and chemokines. Because of the promising outlook for NT-17, the FDA granted orphan drug designation to NT-17 for the treatment of glioblastoma.

**VBI-1901**
Over 90% of glioblastomas express the cytomegalovirus antigens, including gB and pp65, which are often targeted by CD4 and CD8-positive T cells, respectively. VBI-1901 is a vaccine immunotherapeutic consisting of a gB/pp65-enveloped virus-like particle plus adjuvant. A phase 2a trial (NCT03382977) is evaluating VBI-1901 in patients with first-recurrent glioblastoma. Administration route is based on adjuvant: intradermal for GM-CSF (n = 10) or intramuscular for ASO1B (n = 10). OS rates at 12 months were 60% for the GM-CSF arm and 70% for the ASO1B arm, with 18-month rates of 30% and approximately 30% to 40%, respectively. One patient in the GM-CSF arm was progression free at 2 years, and their tumor had reduced in size by 93% from baseline. Immunologic tolerance was not observed with prolonged monthly dosing. Because of promising trial results, the FDA has granted fast track and orphan drug designations to VBI-1901 for glioblastoma treatment. Additionally, the phase 2a study has been expanded, and a VBI-1901 arm has been added to the phase
EXKIVITY® (mobocertinib)
The first and only oral therapy designed to target
EGFR Exon20 insertion+ mNSCLC¹,²
FOR PATIENTS WITH EGFR EXON20 INSERTION+ mNSCLC
POST PLATINUM-BASED CHEMOTHERAPY¹

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLONGATION and TORSADES DE POINTES
See full prescribing information for complete boxed warning.

• EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation.

• Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc.

• Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation.

EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction.
**EGFR Exon20** insertions are distinct targetable driver mutations — **Use an FDA-approved NGS test to identify patients**

EGFR Exon20 insertions are the third most common type of EGFR driver mutation; different from exon 19 deletions and exon 21 L858R mutations, as well as from T790M point mutations⁶,⁷

- ~10% of all EGFR mutations are Exon20 insertions⁷
- About 2,000–4,000 new patients may present in the US every year⁸
- ~50% of patients can be missed by relying on PCR testing*⁵

*PCR can only detect ≤5 out of 60+ EGFR Exon20 insertion variants. The variants detected by PCR are the most common, representing ~50% of cases.³

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**EXKIVITY** is the first and only oral therapy designed to target **EGFR Exon20 insertion+ mNSCLC**¹,²

- National Comprehensive Cancer Network® (NCCN®) recommends mobocertinib as a Category 2A second-line treatment option*²⁹
- Use an FDA-approved NGS test to identify patients in your practice who may benefit from treatment with EXKIVITY⁶

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**WARNINGS AND PRECAUTIONS**

**QTc Prolongation and Torsades de Pointes**

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

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

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Please see Important Safety Information and Brief Summary of full Prescribing Information, including Boxed Warning, on the following pages.
**IMPORTANT SAFETY INFORMATION (CONT’D)**

**Interstitial Lung Disease (ILD)/Pneumonitis**

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

**Cardiac Toxicity**

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

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%), and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY. Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity.

**Diarrhea**

EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population, diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days, but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an anti-diarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity.

**Embryo-Fetal Toxicity**

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

**ADVERSE REACTIONS**

The most common (>20%) adverse reactions are diarrhea (92%), rash (78%), stomatitis (46%), vomiting (40%), decreased appetite (39%), paronychia (39%), nausea (37%), musculoskeletal pain (34%), dry skin (32%), fatigue (29%), pruritus (24%), cough (24%) and decreased weight (21%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (15%), increased amylase (13%), increased lipase (10%), decreased potassium (5.3%), decreased red blood cells (3.5%), increased creatinine (2.7%), decreased magnesium (2.7%), and increased alanine aminotransferase (2.7%).

**DRUG INTERACTIONS**

**CYP3A Inhibitors**

Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations, which may increase the risk of adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs.
CYP3A Inducers
Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations, which may reduce EXKIVITY anti-tumor activity. Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

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

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

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

Females and Males of Reproductive Potential
EXKIVITY can cause fetal harm when administered to pregnant women. Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY.

Advises females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose. Based on animal studies EXKIVITY may impair fertility in males and females of reproductive potential.

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

Geriatric
Of the 114 patients who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence rate of Grade 3 and 4 adverse reactions (69% vs 47%) and serious adverse reactions (66% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-844-217-6468 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION
EXKIVITY™ (MOBOCRERTIN)

These highlights do not include all the information needed to use EXKIVITY safely and effectively. See full prescribing information at EXKIVITYhcp.com

WARNING: QTc PROLONGATION and TORSADES DE POINTES
• QTc can cause life-threatening heart rate-corrected QTc (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolyte correction at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation [see Warnings and Precautions (5.1)].
• Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A4 inhibitors with EXKIVITY, which may further prolong the QTc [see Warnings and Precautions (5.1), Drug Interactions (7.3)].
• Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation [see Dosage and Administration (2.3)].

1 INDICATIONS AND USAGE
EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1), whose disease has progressed on or after platinum-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

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

2.2 Recommended Dosage: The recommended dosage of EXKIVITY is 180 mg orally once daily until disease progression or unacceptable toxicity. Take EXKIVITY with or without food [see Clinical Pharmacology (12.2)], at the same time each day. Swallow EXKIVITY capsules whole. Do not open, chew or dissolve the contents of the capsules.

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time. If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

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

<table>
<thead>
<tr>
<th>Table 1: Recommended EXKIVITY Dose Reductions</th>
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<td>Dose Reductions</td>
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<td>First dose reduction</td>
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<td>Second dose reduction</td>
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Recommended dose modifications of EXKIVITY for adverse reactions are provided in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions (cont'd)</th>
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<tr>
<td>Adverse Reaction</td>
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<tr>
<td>QTc Interval Prolongation and Torsades de Pointes [see Warnings and Precautions (5.1)]</td>
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<td>Grade 3 (QTc interval ≥501 msec or QTc interval increase of &gt;60 msec from baseline)</td>
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<td>Grade 4 (Torsades de Pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia)</td>
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5 WARNINGS AND PRECAUTIONS

5.1 QTc Prolongation and Torsades de Pointes: EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250 patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs) [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)], 12% of patients had a QTc interval ≥500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with a baseline QTc greater than 470 msec. Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A4 inhibitors with EXKIVITY [see Drug Interactions (7.3)], which may further prolong the QTc [see Drug Interactions (7.3)]. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation [see Dosage and Administration (2.3)].

5.2 Interstitial Lung Disease (ILD)/Pneumonitis: EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1), ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed [see Dosage and Administration (2.3)].

5.3 Cardiac Toxicity: EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)], heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure. EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes [see Warnings and Precautions (5.1), Arrhythmia (1.1%), ventricular tachycardia (0.4%), first-degree atrioventricular block (0.4%), second-degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%) and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY. Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity [see Dosage and Administration (2.3)].

UEN = upper limit of normal
* Graded per Common Terminology Criteria for Adverse Events Version 5.0.

2.4 Dosage Modifications for Moderate CYP3A Inhibitors: Avoid concomitant use of moderate CYP3A inhibitors with EXKIVITY. If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce the EXKIVITY dose by approximately 50% (i.e., from 180 to 90 mg, 120 to 60 mg, or 80 to 40 mg) and monitor the QTc interval more frequently. After the moderate CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume EXKIVITY at the dose taken prior to initiating the moderate CYP3A inhibitor [see Drug Interactions (7.3)].
5.4 Diarrhea: EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population (see Adverse Reactions [6.1]), diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake.

Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity (see Dosage and Administration [2.3]).

5.5 Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Oral administration of motocortinib to pregnant rats during the period of organogenesis resulted in embryolethality at maternal exposures 1.7 times the human exposure based on area under the curve (AUC) at the 160 mg once-daily clinical dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY (see Drug Interactions [7.2]) and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY (see Use in Specified Populations [8.1, 8.3]).

6 ADVERSE REACTIONS

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 pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to EXKIVITY as a single agent at a dose of 160 mg orally once daily in 258 patients, including 114 patients with EGFR exon 20 insertion mutation–positively advanced or metastatic NSCLC from Study AP2788-15-101, and patients with other solid tumors. Forty-eight percent (48%) were exposed for 6 months or longer and 12% were exposed for greater than one year. The most common adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain.

The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP2788-15-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXKIVITY (N = 114)</th>
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<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>92</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>46</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>15</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXKIVITY (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>78</td>
</tr>
<tr>
<td>Paronychia</td>
<td>39</td>
</tr>
<tr>
<td>Dry skin</td>
<td>32</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24</td>
</tr>
<tr>
<td>Alopecia</td>
<td>19</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>34</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
</tr>
<tr>
<td>Rinorrhoe</td>
<td>13</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
</tr>
<tr>
<td>Ocular Toxicity</td>
<td>11</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
</tr>
<tr>
<td>QTc interval prolongation</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
</tr>
</tbody>
</table>

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5).

** Events of Grade 3 only (no Grade 4 occurred).

- Stomatitis includes angular cheilitis, aphthous ulcer, cheilitis, moth ulceration, mucosal inflammation, xerostomia, and stomatitis.
- Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.
- Rash includes acne, dermatis, dermatitis axiorm, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and urticaria.
- Paronychia includes nail bed tenderness, nail disorder, nail infection, onycholysis, and paronychia.
- Musculoskeletal pain includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.
- Fatigue includes asthenia, and fatigue.
- Cough includes cough, productive cough, and upper-airway cough syndrome.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.
- Dyspnea includes dyspnea and dyspnea exertional.
- Ocular toxicity includes dry eye, eye pruritis, abnormal sensation in eye, eye discharge, blepharitis, trichiasis, conjunctival hemorrhage, vitreous floaters, blurred vision and corneal edema.
- QTc interval prolongation includes electrocardiogram QT prolonged and ventricular arrhythmia.
- Hypertension includes blood pressure increase and hypertension.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased red blood cells</td>
<td>59</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>25</td>
</tr>
</tbody>
</table>
Implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high-dose level (10 mg/kg).

### 8.2 Lactation

#### Risk Summary

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

#### 8.3 Females and Males of Reproductive Potential

EXKIVITY can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.3)].

#### Pregnancy Testing

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

#### Contraception

- **Females**
  - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective [see Drug Interactions (7.2)].
  - **Males**
    - Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

#### Infertility

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

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

Of the 114 patients (see Clinical Studies [14]) who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (69% vs 47%) and serious adverse reactions (64% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

### 8.6 Renal Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 88 mL/min/1.73 m²) by Modification of Diet in Renal Disease ([MDRD] equation). The recommended dosage of EXKIVITY has not been established for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) [see Clinical Pharmacology (12.3)].

#### 8.7 Hepatic Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN]) and aspartate aminotransferase (AST) ≤ ULN or total bilirubin ≤1 to 1.5 times ULN and any AST or moderate hepatic impairment (total bilirubin 1.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) [see Clinical Pharmacology (12.3)].

### 17 PATIENT COUNSELING INFORMATION

Advises patients to read the FDA-approved patient labeling (Patient Information). QTc Interval Prolongation and Torsades de Pointes

Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see Warnings and Precautions (5.4)].

#### Intestinal Lung Disease (ILD/Pneumonitis)

Inform patients of the risk of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain [see Warnings and Precautions (5.4)].

#### Cardiac Tachycardia

Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see Warnings and Precautions (5.4)].

#### Diarrhea

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

#### Embryo-Fetal Toxicity

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

#### Drug Interactions

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

#### Disposition

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7.3)]. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

#### Missed Dose

Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day [see Dosage and Administration (2.3)].
VAL-083

VAL-083, a bifunctional DNA-targeting agent, causes cell death by creating interstrand DNA cross-links at N7-guanine, culminating in lethal double-strand breaks. Additionally, VAL-083 acts as a radiosensitizer against glioblastoma stem cells in vitro and is not affected by MGMT-mediated chemoresistance per in vitro and in vivo studies. A recent phase 2 trial (NCT03050736) evaluated VAL-083 in combination with radiation therapy in newly diagnosed, MGMT-unmethylated glioblastoma. The initial dose-escalation stage evaluated patients across doses of 20, 30, or 40 mg/m²/day for 3 days every 21 days in combination with standard radiation treatment. In the second, dose-expansion stage, up to 20 additional patients were enrolled at the 30 mg/m²/day dose (total n = 25). The median PFS for all patients was 9.3 months (95% CI, 6.4-12.0), with a median OS of 19.6 months (95% CI, 14.0-22.4). As of the data cutoff, 18 patients (62.1%) had died. Concentrations of VAL-083 in the cerebrospinal fluid were as high or higher compared with plasma. VAL-083 was granted fast track designation by the FDA earlier this year.

Neuroblastoma

The humanized anti-GD2 monoclonal antibody naxitamab (hu3F8; Danyelza) is approved by the FDA in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) as consolidation treatment for chemoresistant high-risk neuroblastoma (HR-NB) that is in remission. However, the approval does not include patients with progressive disease, for whom response to treatment is rare. A recent phase 2 trial (NCT03189706) evaluated the combination of naxitamab, irinotecan, temozolomide, and sargramostim, aka “HITS,” in patients with HR-NB. HITS was administered to 8 patients with HR-NB refractory to induction chemotherapy and 82 patients with up to 6 previous relapses. CRs were observed in 26% of patients, PRs in 11%, and SD in 27%. Objective responses were noted in 64% of all patients, with the following breakdown by patient subgroups: 25% of MYCN-amplified, 100% of refractory, 61% of relapsed, 64% previously receiving irinotecan and temozolomide, 68% previously receiving naxitamab, and 42% previously receiving dinutuximab, irinotecan, and temozolomide. No immunogenicity was observed. These results indicate naxitamab is effective against chemoresistant HR-NB. This agent continues to be evaluated in phase 2 trials.

Other Brain Tumors

Paxalisib

The FDA recently granted orphan drug designation to paxalisib, a PI3K inhibitor that acts upstream of mTOR and easily crosses the BBB. Paxalisib is being investigated in malignant glioma (glioblastoma and diffuse intrinsic pontine glioma). Recently, results were presented at the American Association for Cancer Research 2022 Annual Meeting from 2 different combinations of paxalisib in atypical teratoid/rhabdoid tumors. Paxalisib extended median survival from 40 to 54 days (P = .001) in orthotopic xenograft models of atypical teratoid/rhabdoid tumors and exhibited synergistic effects with TAK580 (a pan-RAF inhibitor that also easily crosses the BBB) to further slow tumor growth. In a separate evaluation, paxalisib also behaved synergistically with the histone deacetylase 1/3 inhibitor RG2833 to decrease cell growth and increase apoptosis. The investigators concluded that these paxalisib-based combinations would make excellent candidates in future clinical trials.

Sonodynamic Therapy

Use of low-intensity ultrasound in combination with sonosensitizers is a potential new modality for treating brain tumors. CV-01 sonodynamic therapy for the treatment of brain cancers is a newer modality being considered across national trial developments in combination with epigenetic modifiers or immuno-therapeutics. “I anticipate this approach being a part of our trial evaluations in the years ahead, but once safety, tolerability, and proper agents have been identified, the question becomes scalability.”

Outlook

Although it appears there are no significant changes coming to the treatment landscape for brain tumors in the next couple of years, Cooney is hopeful for the future. “We’ve entered a hopeful era, to truly reduce morbidity for highly survivable tumors that we haven’t seen before,” she said. “For aggressive tumors we have hope that some of these agents will have a role to play, but that depends on our ability to become quite sophisticated and efficient in trial design and determining exactly what that role is and what the other players are.”

In terms of improving trial design, Cooney discussed the importance of patient engagement in treatment protocols and evaluations. “We are trying to engage the patient and family communities much more in trial design to create protocols that will help us determine the activity of these drugs. Are they getting into the tumor space? What is the mechanism regarding local and systemic effects? This relies on a family’s or patient’s willingness to pursue tumor biopsies or serial [cerebrospinal fluid] collections, but it also speaks to the need for participant-reported outcomes via embedded surveys.” Cooney believes these approaches will allow for more rapid and accurate assessments of the effects of these agents.
Updated Efficacy and Safety Results Support Repotrectinib in ROS1+ NSCLC
By Tony Berberabe, MPH

and recommended phase 2 dose of repotrectinib. Eligible patients had locally advanced or metastatic solid tumors harboring ROS1 or NTRK1-3 gene fusions. Patients received 160 mg of repotrectinib once daily for 14 days, then 160 mg of repotrectinib twice daily.

Four expansion cohorts were identified: expansion 1 included ROS1 TKI-naïve patients (n = 110), expansion 2 included patients with 1 prior ROS1 TKI and 1 prior platinum-based chemotherapy (n = 60), expansion 3 included patients who had 2 prior ROS1 TKIs and no prior chemotherapy (n = 40), and expansion 4 included patients who received 1 prior ROS1 TKI and no prior chemotherapy (n = 60), according to Byoung Chul Cho, MD, PhD, of the Yonsei Cancer Center in Seoul, South Korea.

The primary end point was ORR using RECIST v1.1 criteria, and secondary end points included DOR, clinical benefit rate (CBR), time to response, and ORR in TKI-pretreated patients with tumors harboring ROS1 G2032R. The primary efficacy population includes patients pooled from phases 1 and 2 who began repotrectinib treatment at least 8 months prior to the data cutoff date of June 20, 2022.

Reviewing baseline characteristics across all 4 cohorts, median age was in the 50s and most patients were women who were never smokers. Regarding prior TKI use, in cohort 4 (n = 56), 82% received crizotinib (Xalkori) and 16% were treated with entrectinib (Rozlytrek). In cohort 2 (n = 26), 81% received crizotinib and 15% were treated with entrectinib. In cohort 3, 100% received crizotinib, 71% received lorlatinib (Lorbrena), and 17% received entrectinib.

Treatment Responses
In TKI-naïve patients with ROS1-positive advanced NSCLC, after a median follow-up of 18.1 months, ORR was 78.9% (95% CI, 67.6%-87.7%) with 4 (5.6%) complete responses (CRs) and 52 (73.2%) partial responses (PRs). In this cohort, the CBR was 94.4% (95% CI, 86.2%-98.4%).

For all treated patients (n = 71), the median DOR was 13.3 months (range, 0.80-60.6+). Sixty-three percent of patients remained on treatment. Among all patients with a CR (n = 56), the median DOR was 15.5 months (range, 3.1-60.6+) with 75% of patients remaining on treatment.

“At a median follow-up of 18.1 months, DOR and PFS [progression-free survival] data are still immature,” Cho said. “The DOR and PFS at 12 months were 86% and 79%, respectively.”

In the cohort of patients pretreated with 1 TKI and no prior chemotherapy, after a median follow-up of 15.5 months, the ORR was 37.5% (95% CI, 24.9%-51.5%). Three patients (5.4%) had a CR and 18 (32.1%) had a PR. The CBR in this cohort was 89.1% (95% CI, 69.6%-91.1%).

For all treated patients (n = 56), median DOR was 8.3 months (range, 0.50-24.8+) with 34% of patients...
remaining on treatment. Of all patients with a CR (n = 21), median duration of treatment was 11.2 months (range, 5.6-21.3) with 57% remaining on treatment.

In patients pretreated with 1 TKI and no prior chemotherapy, after a median follow-up of 15.5 months, the DOR rate was 79.5% and PFS rate was 67.4%.

In cohort 2, after a median follow-up of 15.5 months, the DOR rate was 79.5% and PFS rate was 67.4%.

In cohort 3, after a median follow-up of 21.3 months, the ORR rate was 42.3% (95% CI, 23.4%-63.1%) with 1 CR and 10 PRs. The DOR rate of 6 months or more was 64% (95% CI, 35.2%-92.1%), PFS rate at 6 months or greater was 38.9% (95% CI, 19.4%-58.4%).

In patients with a ROS1 G2032R resistance mutation, the ORR rate was 58.8% (95% CI, 32.9%-81.6%) with 1 CR and 9 PRs. The CBR rate was 70.6% (95% CI, 44.0%-89.7%), and DOR rate of 6 months or more was 70% (95% CI, 41.6%-98.4%).

Regarding safety, the most common treatment-emergent adverse event (TEAE) was low-grade dizziness (61.3%), which was grade 1 in 73.2% of patients. Overall, 19.6% of patients reported ataxia, with 20 patients (4.5%) reporting ataxia in the absence of dizziness.

Cho added that 45% of patients had TEAEs leading to drug interruption, 34% had TEAEs leading to dose reductions, and 9.7% had TEAEs leading to drug discontinuation.

Global health status and QOL were also assessed. Cho said median time to first improvement was observed at 3.71 months for global health status and 4.69 months for QOL. “These updated findings suggest that repotrectinib could represent a potential new treatment option for patients with ROS1-positive advanced NSCLC,” Cho concluded. TT

**REFERENCE**

overexpression or fusion. The majority were male (64%), the median age was 56 years (range, 38-79), and patients had a ECOG performance status of either 0 (29%) or 1 (71%).

As of October 21, 2022, 55% of patients were still undergoing treatment and had completed a median of 4 cycles (range, 1-12). “Our longest-treated patients are now reaching about 36 weeks on study,” Gibson said.

Response data for 23 patients show an ORR of 39% and a disease control rate (DCR) of 83%. Gibson noted that all responses were partial responses.

In patients with HER2-positive NSCLC (n = 14), the ORR was 50% and the DCR was 93%. Responses were reported across a wide range of dosing schedules and dose levels.

In 17 patients following the twice-a-day dosing schedule, Gibson reported encouraging safety results, with 1 patient experiencing a grade 3 or greater treatment-related adverse event (TRAE) and 1 patient having to reduce their dose because of a TRAE. There were no TRAEs leading to discontinuation.

The most common TRAE was diarrhea (n = 7) with 6 patients with grade 1 severity and 1 patient with grade 2 severity. Gibson noted that 1 patient developed grade 2 edema during cycle 4 of treatment.

Regarding AEs, 1 patient experienced a grade 3 or greater TRAE, with no cases of dose reduction, discontinuation, or DLTs reported. One patient developed grade 3 anemia and is being assessed for treatment relatedness, Gibson said.

In summary, MTD has not been reached with either twice daily or daily dosing schedule and manageable adverse events have been observed.

“We have not reached the maximum tolerated dose on either the twice a day or once daily schedule,” Gibson said. “Only 1 dose limiting toxicity has been observed to date and this was a grade 2 edema. We believe BI 1810631 has demonstrated encouraging anti-tumor activity.”

Although pharmacokinetic data and biomarker analysis were not presented because of lack of time, the investigators plan to publish these findings in the near future, Gibson concluded. TT

REFERENCE


A NOVEL MPS1 INHIBITOR, NMS-01940153E (S81694), has demonstrated clinical activity in patients with relapsed or refractory unresectable hepatocellular carcinoma (HCC), according to the phase 1 results of a phase 1/2 trial (MPSA-153-001). The data were presented at the 2022 European Organisation for Research and Treatment-National Cancer Institute-American Association for Cancer Research (EORTC-NCI-AACR) Symposium on Molecular Targets and Cancer Therapeutics.

Maria Reig, MD, PhD, head of the Hepatic Oncology Unit at the Hospital Clínico de Barcelona, Spain, explained that the MPS1 kinase regulates the spindle assembly checkpoint, and when it is inhibited, it leads to cancer death because of excess mitotic instability. There is a high unmet need for new therapies with novel mechanisms in the third-line setting and high expression of MPS1 has been found in HCC compared with normal tissue (P = .003), and MPS1 was found to be an independent prognostic factor for overall survival in HCC (HR, 1.92; 95% CI, 1.01-3.68).²

Reig presented new preclinical data showing that NMS-01940153E is highly active specifically in HCC cell lines. Compared with traditional therapies for HCC, including regorafenib (Stivarga), lenvatinib (Lenvima), sorafenib (Nexavar), and doxorubicin, NMS-01940153E demonstrated high sensitivity and a low half maximal inhibitory concentration (< 0.05 μM) across 7 HCC cell lines.³

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In data from a first-in-human study (ISRCTN35641359) of the MPS1 inhibitor in patients with advanced solid tumors, among 35 evaluable patients, 2 patients showed a response and 13 had stable disease. Both

CONTINUED ON PAGE 35
1L aRCC treatment that offers a balance of data:
superior OS, safety and tolerability, and patient-reported quality of life1-4

*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; P=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.1,2

**INDICATIONS**
CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

**IMPORTANT SAFETY INFORMATION**
**WARNINGS AND PRECAUTIONS**
**Hemorrhage:** Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

**Perforations and Fistulas:** Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

**Thrombotic Events:** CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

**Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information throughout and Brief Summary of the Prescribing Information for CABOMETYX on following pages.
Superior PFS and ORR results in the ITT population in the primary analysis¹

Median follow-up time of 18.1 months; range: 10.6-30.6 months²

**Primary endpoint**

<table>
<thead>
<tr>
<th>MEDIAN PFS WAS DOUBLED*</th>
<th>ORR WAS DOUBLED**</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.6 months CABOMETYX + OPDIVO</td>
<td>55.7% CABOMETYX + OPDIVO</td>
</tr>
<tr>
<td>HR=0.51 (95% CI: 0.41-0.64) P&lt;0.0001</td>
<td>(95% CI: 50.1-61.2; n=328)</td>
</tr>
</tbody>
</table>

*PFS and ORR were assessed by BICR.¹

**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS**

**Diarrhea:** Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to Grade 1, resume at a reduced dose.

**Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Hepatotoxicity:** CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

**Adrenal Insufficiency:** CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 9.8% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

**Proteinuria:** Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, ostiitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

**Impaired Wound Healing:** Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

**Thyroid Dysfunction:** Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients. Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

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Early and sustained separation of OS curves in the primary analysis\(^1\)

**CheckMate-9ER study design\(^{1,2,5}\)**

A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. PFS and ORR were assessed by BICR. Quality of life was evaluated as an exploratory endpoint using the FKiS-19 scale, and the clinical significance is unknown. Other exploratory endpoints included biomarkers, PK, immunogenicity, and PFS-2. An updated efficacy analysis was conducted when 271 events were observed based on the pre-specified number of events for the pre-planned final analysis of OS.

**Hypocalcemia:** CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN. In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients. Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

**Embryo-Fetal Toxicity:** CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

**ADVERSE REACTIONS**

The most common (≥20%) adverse reactions are: CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

**DRUG INTERACTIONS**

**Strong CYP3A4 Inhibitors:** If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

**Strong CYP3A4 Inducers:** If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John’s wort.

**USE IN SPECIFIC POPULATIONS**

**Lactation:** Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

**Hepatic Impairment:** In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

**You are encouraged to report negative side effects of prescription drugs to the FDA.** Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on following pages.

**References:**

1. CABOMETYX* (cabozantinib) Prescribing Information. Exelixis Inc; 2022.
CABOMETYX® (cabozantinib) TABLETS
BRIEF SUMMARY OF PRESCRIBING INFORMATION. PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION. INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differentiated Thymic Cancer
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thymic ductal carcinoma (TDC) that has progressed following prior VEGF-targeted therapy and who are radioactive iodine-refractory or ineligible.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in the RCC, HCC, and DTC studies.

Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hematomas, hemostasis, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscesses and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop an acute myelocytic infarction or serious arterial or venous thrombotic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension and may result in a hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and 11% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Without CABOMETYX, for hypertension that is not adequately controlled with medical management: when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX.

Monitor and manage patients using anti-diarrheals as indicated. Without CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 8.5% of patients treated with CABOMETYX, 2% of patients treated with nivolumab, and 15% of patients treated with CABOMETYX plus nivolumab. Patients with any Grade 3-4 PPE that occurred in ≥1% of patients: Palmar-plantar erythrodysesthesia, Hypothyroidism, Nervous system disorders, Skin and Subcutaneous Tissue Disorders, and Blood and Lymphatic System Disorders.

CABOMETYX can cause PPE. Monitor blood calcium levels and replace calcium as necessary during treatment. Without CABOMETYX until resolved or reduced at a dose above recovery or permanently discontinue CABOMETYX depending on severity.

5.7 Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. CABOMETYX is not recommended for use in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertensive and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hypothyroidism, Nervous System disorders, Skin and Subcutaneous Tissue Disorders, and Blood and Lymphatic System Disorders. Other clinically important adverse reactions (all grades) that were reported in <10% of patients in the CABOMETYX monotherapy trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=311)</th>
<th>Everolimus (n=317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Percentage (%) of Patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Increased AST</th>
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<th>3</th>
<th>40</th>
<th>9</th>
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<tbody>
<tr>
<td>Increased ALT</td>
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<td>32</td>
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<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
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<td>1</td>
<td>70</td>
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<tr>
<td>Increased lipids</td>
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<tr>
<td>Hypertension</td>
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<td>3</td>
<td>5</td>
<td>12</td>
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<tr>
<td>Hyperglycemia</td>
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<td>2</td>
<td>25</td>
<td>11</td>
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<td>Hypokalemia</td>
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<td>3</td>
<td>14</td>
<td>6</td>
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<tr>
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<td>28</td>
<td>4</td>
<td>6</td>
<td>3</td>
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<tr>
<td>Hypercalcemia</td>
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<td>5</td>
<td>43</td>
<td>9</td>
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<tr>
<td>Leukopenia</td>
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<td>5</td>
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<tr>
<td>Neutropenia</td>
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<td>4</td>
<td>1</td>
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<tr>
<td>Lymphopenia</td>
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<td>11</td>
<td>27</td>
<td>11</td>
<td></td>
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<tr>
<td>Hematocrit</td>
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<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10</td>
<td>1</td>
<td>10</td>
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</table>

CABOMETYX was evaluated in CABOMETYX, a randomized, open-label trial in patients with previously untreated advanced RCC. In the trial in patients with advanced renal cell carcinoma, in which 297 patients were exposed to treatment for >1 year.

Adverse Reaction | CABOMETYX (n=331) | Everolimus (n=322) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Percentage (%) of Patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 15.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 31 months (range 0.2 – 25.5) for patients receiving sunitinib. Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥20%) in patients treated with CABOMETYX were hypertension, diarrhea, hypokalemia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypertension, and syncope. The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding standard treatment), and the dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥2% of Patients Who Received CABOMETYX in CABOSUN

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=78)</th>
<th>Placebo (n=72)</th>
<th>Percentage (% of Patients)</th>
<th>Patients with Any Grade 3-4 Adverse Reaction</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td></td>
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<tr>
<td>Hypokalemia</td>
<td>2</td>
<td>2</td>
<td>2.8</td>
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<tr>
<td>Nausea</td>
<td>23</td>
<td>20</td>
<td>26.5</td>
<td></td>
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<tr>
<td>Abdominal Pain</td>
<td>22</td>
<td>19</td>
<td>24.1</td>
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<tr>
<td>Vomiting</td>
<td>17</td>
<td>19</td>
<td>23</td>
<td></td>
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<tr>
<td>Dyspepsia</td>
<td>15</td>
<td>16</td>
<td>20.3</td>
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<tr>
<td>General</td>
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</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>7</td>
<td>8.4</td>
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</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>6</td>
<td>8.3</td>
<td></td>
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<tr>
<td>Metabolism and Nutrition</td>
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<td>Hypothyroidia</td>
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<tr>
<td>Decreased appetite</td>
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<td>7</td>
<td>9.8</td>
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<tr>
<td>Diarrhea</td>
<td>3</td>
<td>5</td>
<td>6.9</td>
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<td>Hypokalemia</td>
<td>3</td>
<td>4</td>
<td>5.5</td>
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<td>Hypophosphatemia</td>
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<td>7</td>
<td>9.9</td>
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<tr>
<td>Hypoglycemia</td>
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<td>10.9</td>
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<td>Hyperphosphatemia</td>
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<td>3</td>
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<tr>
<td>Skin and Subcutaneous Tissue</td>
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<td>Palmoplantar erythrodysesthesia</td>
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<td>Hematological</td>
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<td>Anemia</td>
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<td>Thrombocytopenia</td>
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<td>3.6</td>
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<td>Nervous System</td>
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<td>Cough</td>
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<tr>
<td>Dysphonia</td>
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<td>3</td>
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<tr>
<td>Infections and Infections</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>20</td>
<td>10</td>
<td>13.1</td>
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Table 4. Adverse Reactions in ≥25% of Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=320)</th>
<th>Nivolumab (n=320)</th>
<th>Percentage (% of Patients)</th>
<th>Patients with Any Grade 3-4 Adverse Reaction</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
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<tr>
<td>Diarrhea</td>
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<td>70.3</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td>59.4</td>
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<td>Diarrhea</td>
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<td>Stomatitis</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Hypophosphatemia</td>
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<td>Hypomagnesemia</td>
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<td>Respiratory, Thoracic, and Mediastinal</td>
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<td>Fatigue</td>
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<td>Dysphonia</td>
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<td>Infections and Infections</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<td>16</td>
<td>53.1</td>
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Table 5. Laboratory Values Worsening from Baseline Occurring in ≥20% of Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Laboratory Abnormality</th>
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<tbody>
<tr>
<td>CABOMETYX and Nivolumab</td>
<td>CABOMETYX and Nivolumab</td>
</tr>
<tr>
<td>Grades 1-4</td>
<td>Grades 3-4</td>
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<tr>
<td>Percentage (% of Patients)</td>
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</table>

Table 6. Adverse Reactions Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=487)</th>
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<tr>
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</tr>
<tr>
<td>Diarrhea</td>
<td>54</td>
<td>19</td>
<td>22.8</td>
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<tr>
<td>Nausea</td>
<td>24</td>
<td>12</td>
<td>14.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>12</td>
<td>16.8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>22</td>
<td>12</td>
<td>16.8</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>52</td>
<td>28</td>
<td>21.0</td>
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<tr>
<td>Hypothyroidia</td>
<td>42</td>
<td>21</td>
<td>16.8</td>
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<tr>
<td>Hypothyroidia</td>
<td>42</td>
<td>21</td>
<td>16.8</td>
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<tr>
<td>Hypokalemia</td>
<td>22</td>
<td>12</td>
<td>16.8</td>
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<tr>
<td>Hypophosphatemia</td>
<td>37</td>
<td>21</td>
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<td>Hypoglycemia</td>
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<td>10</td>
<td>14.0</td>
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<td>Dysphonia</td>
<td>15</td>
<td>5</td>
<td>10.9</td>
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<tr>
<td>Infections and Infections</td>
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<td></td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>59</td>
<td>21</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Table 7. Laboratory Abnormalities Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Laboratory Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABOMETYX and Nivolumab</td>
<td>CABOMETYX and Nivolumab</td>
</tr>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Percentage (% of Patients)</td>
<td></td>
</tr>
</tbody>
</table>

Table of Adverse Reactions in ≥25% of Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER
The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 103 patients with advanced differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.0 – 11.0) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 56% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaskan Native, and 63% received prior iodine-131.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPI, fatigue, hypertension, and stomatitis. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, fatigue, hypertension, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in ≥ 2% of patients were PPI, diarrhea, fatigued, proteinuria, and decreased appetite. Dose interruptions occurred in 72% patients receiving CABOMETYX. The most common laboratory abnormalities occurring in 5% of patients receiving CABOMETYX were PPE, diarrhea, proteinuria, and decreased appetite. Dose interruptions occurred in 25% of patients receiving CABOMETYX.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=125) All Grades Grade 3 or 4 Placebo (n=62) All Grades Grade 3 or 4</th>
<th>Percentage (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased alanine aminotransferase</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased hemoglobin</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Decreased hematocrit</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased international normalized ratio</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased neutrophils</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
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<tr>
<td>Increased total bilirubin</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>16 2 9 2</td>
<td>9 2 4 1</td>
</tr>
</tbody>
</table>

Note: Laboratory abnormalities are shown that increased or decreased from ≥ 2% in any grade (≥ 2% in any grade) or ≥ 2% in grade 3 (≥ 2% in grade 3) for patients receiving CABOMETYX and for patients receiving placebo.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=125) All Grades Grade 3 or 4 Placebo (n=62) All Grades Grade 3 or 4</th>
<th>Percentage (% of Patients)</th>
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<tbody>
<tr>
<td>Hematology</td>
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<tr>
<td>Leukocyte count decreased</td>
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<td>2 0 0 0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>38 7 2 1</td>
<td>2 0 0 0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>26 5 2 1</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Increased hemoglobin</td>
<td>8 2 1 0</td>
<td>0 0 0 0</td>
</tr>
</tbody>
</table>

Note: Laboratory abnormalities are shown that increased or decreased from ≥ 2% in any grade (≥ 2% in any grade) or ≥ 2% in grade 3 (≥ 2% in grade 3) for patients receiving CABOMETYX and for patients receiving placebo.

**7 DRUG INTERACTIONS**

**7.1 Effects of Other Drugs on CABOMETYX**

CABOMETYX is a potent inhibitor of the type I and type II activation of VEGF receptors (VEGFR), FLT3 receptors, and PDGFR receptors, acting as an ATP-competitive inhibitor of VEGFR2, VEGFR1, and FLT3.

CABOMETYX inhibits the activity of VEGFR2 in vitro with IC50 values of 0.6 nM (measured with VEGF165), 1.6 nM (measured with VEGF121), and 2.1 nM (measured with VEGF165 and VEGF121).

CABOMETYX inhibits the activity of FLT3 in vitro with IC50 values of 0.6 nM (measured with FLT3 ligand), 5.0 nM (measured with FLT3 ligand and FLT3 ligand plus VEGF165), and 10.0 nM (measured with FLT3 ligand and FLT3 ligand plus VEGF165 and VEGF121).

CABOMETYX inhibits the activity of PDGFRB in vitro with IC50 values of 0.6 nM (measured with PDGF-BB) and 5.0 nM (measured with PDGF-BB and PDGF-AA).

CABOMETYX inhibits the activity of Tie2 in vitro with IC50 values of 0.6 nM (measured with Ang1) and 5.0 nM (measured with Ang1 and Ang2).

CABOMETYX inhibits the activity of FGFR1 in vitro with IC50 values of 0.6 nM (measured with FGF2 and FGF4) and 5.0 nM (measured with FGF2 and FGF4 plus PPF1).
Patients with HCC in the study had stable disease lasting 6 months, and 1 had a transient reduction in liver target lesion size of 27% after having received 3 prior systemic therapies. The MPSA-153-001 trial is a dose-finding and dose-expansion study in patients with unresectable HCC who were previously treated with systemic therapy. In phase 1, patients were enrolled if they had failed standard treatment options to determine the maximum tolerated dose and recommended phase 2 dose for the agent. In the ongoing phase 2 portion of the trial, up to 40 patients who were being treated in the third line or beyond were included.

Patients received NMS-01940153E intravenously at either 100 mg/m² (n = 6) or 135 mg/m² (n = 6) on days 1, 8, and 5 of each cycle. Treatment continued until disease progression or treatment intolerance.

Twelve evaluable patients have been studied to date in the phase 1 portion who have a median age of 64 years (range, 28-76) and 91.7% are male. Half the patients have locally advanced disease and the other half have metastatic disease. The most common metastatic site was the lung, followed by the lymph nodes, for 25%, and the other half have metastatic disease. The most common prior therapies including sorafenib (75%), cabozantinib (Cabometyx; 33.3%), regorafenib (25%), and lenvatinib (25%). As of the data cutoff, 2 patients achieved a partial response, 1 in each dose group, and 3 had stable disease. Of the 2 responders, the duration of response was 2.6 months for 1 patient and 9.3 months for the other. Two patients, 1 in each group, are receiving ongoing treatment. Among 7 patients evaluable for α-fetoprotein, 3 experienced a decrease in levels of at least 20%.

Reig noted that 1 patient who experienced a partial response and a duration of response of 9.3 months had a reduction in lesion size of 44% from baseline. The patient was still alive at 12.3 months from study entry.

“This is something completely unexpected in our field, and that’s why we believe that in spite of the small sample of this trial, we have a sign of activity,” she said.

The most common adverse events (AEs) reported were neutropenia in 50% of patients, platelet count decrease in 25%, and diarrhoea in 25%. In the 100-mg/m² dose group, only 2 grade 3 events of neutropenia and 1 grade 4 event of sepsis were observed. AEs were more common in the 135-mg/m² dose group, with 5 grade 3 events (neutropenia, platelet count decrease, asthenia, and systemic hypertensive crisis) and 2 grade 4 events (neuropenia), which were considered dose-limiting toxicities.

One discontinuation was due to an AE (grade 3 asthenia and platelet count decrease) in the 135-mg/m² group. One patient in the 100-mg/m² group had a treatment interruption in the first cycle due to an infusion reaction. As a result, the maximum tolerated dose was determined to be 100 mg/m² per week. TT
In the nivolumab/ipilimumab arm, responders experienced a PR, 20% of patients had stable disease, and 60% of patients experienced disease progression (FIGURE). The disease control rate was 79% in the CBM588 arm compared with 20% in the nivolumab/ipilimumab arm ($P = .004$).

“Although limited by the sample size, the combination of nivolumab, ipilimumab, and CBM588 demonstrated superior clinical outcomes over nivolumab/ipilimumab. PFS [progression-free survival] and ORR with nivolumab, ipilimumab, and CBM588 also exceeded those observed with nivolumab/ipilimumab in historical datasets,” lead study author Nazli Dizman, MD, a hospital resident at the Yale School of Medicine, said in a presentation.

CBM588 is a live bacterial product that contains Clostridium butyricum, an anaerobic spore-forming bacterium commonly used and studied in gastrointestinal conditions in Japan. A retrospective analysis of 118 patients with non–small cell lung cancer showed those who received CBM588 before and/or after immune checkpoint inhibitors had an ORR of 48% and complete response (CR) rate of 8% compared with an ORR of 25% and no CRs for patients given immune checkpoint inhibitors alone.²

The phase 1b trial evaluated the efficacy and safety of nivolumab/ipilimumab with or without CBM588 in patients with RCC who had measurable metastatic...
The most common metastatic sites included the lung (68% and 60%, respectively), lymph node (42% and 70%), bone (37% and 40%), soft tissue (37% and 30%), liver (16% and 20%), and pancreas (16% and 10%).

Additional data showed that patients in the CBM588 arm achieved a median PFS of 36.4 months (95% CI, 9.4-63.3) compared with 2.5 months (95% CI, 2.0-2.9) for those in the nivolumab/ipilimumab arm (HR, 0.10; 95% CI, 0.03-0.33; P < .001). The median duration of response in the CBM588 arm was 30.7 months vs 4.5 months in the control arm. The median overall survival was not reached in either arm. In the CBM588 arm, 82.8% of patients were alive at the time of data cutoff.

Regarding safety, at least 1 adverse event (AE) of any grade was reported in 100% of patients in the CBM588 arm compared with 90% in the nivolumab/ipilimumab arm. AEs of grade 2 or above occurred in 63% and 50% of patients in the CBM588 and nivolumab/ipilimumab arms, respectively.

Two instances (11%) of grade 3 nephritis were reported in the CBM588 arm, and grade 3 events of adrenal insufficiency, fatigue, maculopapular rash, arthritis/arthralgia, diarrhea, acute kidney injury, abdominal pain, transaminitis, glucose intolerance, increased alkaline phosphatase levels, pancreatitis, acidosis, and chest wall pain each occurred in 1 patient. One instance of grade 4 decreased neutrophil count was reported in 1 patient in the CBM588 arm. No AEs of grade 4 or above were observed in the nivolumab/ipilimumab arm.

A randomized, double-blind phase 3 study will compare the combination of nivolumab/ipilimumab plus CBM588 or placebo as a frontline treatment for patients with intermediate- or high-risk advanced clear cell RCC.

“Larger efforts investigating the impact of CBM588 on clinical outcomes are underway. We are devoting our efforts to better understand the mechanism of action of CBM588 by studying metabolic samples in patients and in mice,” Dizman concluded.

REFERENCES


Combination immunoncology (IO) regimens are a staple in the frontline treatment of renal cell carcinoma (RCC). Specifically, doublet IO therapy with ipilimumab (Yervoy) and nivolumab (Opdivo) is an FDA-approved option, and triplet immunotherapy, consisting of IO plus a VEGF inhibitor or other drug, has shown to be effective in first-line RCC clinical trials. Oncologists question whether the efficacy is enhanced with triplet vs doublet therapy and if safety/tolerability is decreased.

During a debate at the 2022 International Kidney Cancer Symposium: North American, Yousef Zakharia, MD, a medical oncologist, clinical associate professor, director of the Phase 1 Program, and coleader of the Genitourinary Oncology Program at University of Iowa Hospitals & Clinics in Iowa City, gave a presentation favoring doublet IO for first-line RCC. In opposition, Rana R. McKay, MD, a medical oncologist and associate professor of medicine at UC San Diego Health, presented a case in favor of triplet therapy.

Less is More
According to Zakharia, doublet combinations are the gold standard in first-line RCC, but a case can be made for triplet therapy in select subgroups. Patients who may benefit from a doublet IO regimen up front are those with intermediate- or poor-risk RCC, specifically with sarcomatoid features.

“Whether IO/IO or IO/TKI [tyrosine kinase inhibitor], doublets remain the standard of care in the first-line setting,” Zakharia said during his presentation. “[For] triplet combinations, even if [they] become FDA approved, I would like to have very careful conversations with my patients. We would like to see more survival data, and I’m hopeful for the future [that] we will be discussing more biomarker-driven arguments.”

Various clinical trials have shown that combining multiple IO agents or combining IO agents with TKIs provides good survival and responses in first-line RCC. In KEYNOTE-427 (NCT02853344), CheckMate 214 (NCT02231749), KEYNOTE-426 (NCT02853331), CHECKMATE 9ER (NCT03141177), and CLEAR (NCT02811861), the median progression-free survival (PFS) with doublet therapy ranged from 11.6 months to 17.5 months. Zakharia’s argument in favor of doublet therapy was supported by results from CheckMate 214.

CheckMate 214
The phase 3, randomized, open-label CheckMate 214 study assessed 1096 patients with previously untreated advanced clear cell RCC. The patients were randomly assigned 1:1 to receive 3 mg/kg nivolumab (Opdivo) in combination with 1 mg/kg ipilimumab (Yervoy; ipi/nivo) or 50-mg sunitinib (Sutent) monotherapy. The coprimary end points evaluated in the study were overall survival (OS), objective response rate (ORR), and PFS in the intermediate- to poor-risk group.

Overall, 550 patients were treated with doublet IO therapy and 546 received single-agent sunitinib. There were 425 patients in the doublet IO arm and 422 patients in the sunitinib arm who had intermediate- to poor-risk disease.

At a median follow-up of 25.2 months in the intermediate- to poor-risk subgroup population, the 18-month OS rate was 75% (95% CI, 70%-78%) with the combination vs 60% (95% CI, 55%-65%) with sunitinib. Median OS was not reached with IO therapy compared with 26.0 months in the sunitinib arm (HR, 0.63; P < .001). The ORR in the IO
arm was 42% vs 27% with sunitinib (P<.001), and complete responses were observed in 9% and 1%, respectively. Ipi/nivo showed a median PFS of 11.6 months compared with 8.4 months in the sunitinib arm (HR, 0.82; P=.03). The results did not cross the threshold for significant PFS improvement.

Ninety-three percent of patients who received the IO doublet experienced treatment-related adverse events (TRAEs) vs 97% of the sunitinib arm, and the TRAEs were high grade in 63%, respectively. TRAEs led to treatment discontinuation in 22% of patients in the doublet IO arm vs 12% in the IO monotherapy arm.

“The other [outcome] CheckMate 214 has set up, nowadays, is the 5-year overall survival. In intermediate- and poor-risk [disease], you’re seeing that, at 5 years, 43% of those patients are still alive...You might argue these patients are technically cured with ipi/nivo,” Zakharia said. “We have a median overall survival of 47 months. This is very intriguing, and the data [get] even more intriguing in sarcomatoid features.”

In the sarcomatoid population, median follow-up was 42 months in a post hoc analysis of CheckMate 214. In 139 patients, the median OS was not reached in the doublet IO arm (95% CI, 25.2-not estimable) compared with 14.2 months (95% CI, 9.3-22.9) in the sunitinib arm (HR, 0.45; 95% CI, 0.3-0.7; P=.0004). The median PFS in patients with sarcomatoid RCC was 26.5 months with doublet IO vs 5.1 months with single-agent IO (95% CI, 7.7-18.2) in the doublet arm (HR, 0.73, 95% CI, 0.57-0.94; P=.0093).

Zakharia noted a newly launched, investigator-initiated study of pembrolizumab (Keytruda) plus axitinib (Inlyta) and high-dose selenium in the form of seleno-L-methionine in first-line metastatic RCC at the University of Iowa.

### Rationale for More Agents Up Front

McKay explained that there is evidence to support the use of triplet therapy in RCC. Research shows that combining the IO combination of ipi/nivo with the TKI cabozantinib (Cabometyx) prolongs PFS and decreases the rate of progressive disease while increasing responses compared with doublet IO. She said research also shows that the triplet therapy has a manageable safety profile.

“The IO/VEGF TKIs are a winner in the short game,” McKay said during her presentation. “They have great up-front responses of over 50%. The PFS is great, but we’re still lacking data on long-term durability and whether we cure patients with IO/VEGF therapy. With ipi/nivo, the Achilles’ heel of that regimen is at the primary [progressive disease] rate, which is around 20%. However, what we all hope for our patients is that we can cure them. There’s a tail on the curve, which we’ve seen with over 5 years of follow-up data; the PFS curves hold steady right at 30%.”

Data supporting McKay’s argument were from the phase 3 COSMIC-313 study (NCT03937219).

### COSMIC-313

COSMIC-313 included 855 patients who were randomly assigned 1:1 to receive cabozantinib with ipi/nivo (n=428) or ipi/nivo alone (n=427). Of the patients enrolled, 75% of the triplet arm were classified as intermediate- to poor-risk compared with 25% of the doublet arm.

The median PFS observed was not reached with the triplet regimen (95% CI, 14.0-not estimable) compared with 11.3 months (95% CI, 14%-35%); P=.013). Additionally, objective responses were observed in 43% (95% CI, 37.2%-49.2%) of the triplet arm vs 36% (95% CI, 30.1%-41.8%) in the doublet arm. The median duration of response was not reached in either treatment arm. Patients had higher ORRs with nivolumab plus ipilimumab vs sunitinib (60.8% [95% CI, 49%-72%] vs 23.1% [95% CI, 14%-35%]; P<.0001), with 18.9% and 3.1% of patients achieving complete responses, respectively (TABLE).4

The triplet regimen led to grade 3/4 TRAEs in 73% of patients compared with 41% in the doublet arm. TRAEs led to discontinuation of all treatment components in 12% of the triplet arm vs 5% of the doublet arm.

McKay asked, “How can we get the best of both worlds with wins in the short game and wins in the long game? How can we decrease the [progressive disease] rate and potentially offer long-term durability and offer up-front primary tumor reduction?” She explained that this is where triplet therapy comes into play.

### References


### Table: ORR per IRCC and by baseline tumor PD-L1 expression level in COSMIC 313

<table>
<thead>
<tr>
<th></th>
<th>PATIENTS WITH sRCC AND I/P-RISK DISEASE</th>
<th>PATIENTS WITH sRCC AND TUMOR PD-L1 ≥ 1%</th>
<th>PATIENTS WITH sRCC AND TUMOR PD-L1 &lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab + ipilimumab (n=74)</td>
<td>Sunitinib (n=65)</td>
<td>Nivolumab + ipilimumab (n=36)</td>
</tr>
<tr>
<td>Confirmed ORR (95% CI), %</td>
<td>61 (49-72)</td>
<td>23 (14-35)</td>
<td>69 (52-84)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>Not calculated</td>
<td>Not calculated</td>
</tr>
</tbody>
</table>

P value: Complete overall response, n (%)

Complete response 14 (19) 2 (3) 8 (22) 1 (3) 6 (17) 1 (3)
Partial response 31 (42) 13 (20) 17 (47) 7 (21) 13 (37) 5 (17)
Stable disease 8 (11) 26 (40) 4 (11) 12 (36) 4 (11) 12 (41)
Progressive disease 15 (20) 15 (23) 5 (14) 10 (30) 9 (26) 5 (17)
Unable to determine/ not reported 6 (8) 9 (14) 2 (6) 3 (9) 3 (9) 6 (21)

I/P: intermediate/poor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IRRC, independent radiology review committee; ORR, objective response rate; sRCC, sarcomatoid renal cell carcinoma.
dMMR Recurrent or Advanced Endometrial Cancer ILLUMINATED

INDICATION

JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions
- Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue and can occur at any time during or after treatment with a PD-1/PD-L1–blocking antibody, including JEMPERLI.
- Monitor closely for signs and symptoms of immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. For suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Based on the severity of the adverse reaction, withhold or permanently discontinue JEMPERLI. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to ≤ Grade 1. Upon improvement to ≤ Grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Immune-Mediated Pneumonitis
- JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. 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. Pneumonitis occurred in 1.4% (7/515) of patients, including Grade 2 (1.2%) and Grade 3 (0.2%) pneumonitis.

Immune-Mediated Colitis
- Colitis occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis. In such cases, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis
- JEMPERLI can cause immune-mediated hepatitis, which can be fatal. Grade 3 hepatitis occurred in 0.2% (1/515) of patients.

Immune-Mediated Endocrinopathies
- Adrenal Insufficiency
  - Adrenal insufficiency occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Hypophysitis
  - JEMPERLI can cause immune-mediated hypophysitis. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Thyroid Disorders
  - Thyroiditis occurred in 0.4% (2/515) of patients; both were Grade 2. Hypothyroidism occurred in 7.2% (37/515) of patients, all of which were Grade 2. Hyperthyroidism occurred in 1.9% (10/515) of patients, including Grade 2 (1.7%) and Grade 3 (0.2%). Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis
  - JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Nephritis with Renal Dysfunction
- JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis occurred in 0.4% (2/515) of patients; both were Grade 2.

Immune-Mediated Dermatologic Adverse Reactions
- JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rash. Withhold or permanently discontinue JEMPERLI depending on severity.

Learn more about JEMPERLI at JEMPERLIHCP.COM
JEMPERLI has demonstrated clinically meaningful efficacy¹,²

**Primary efficacy analysis (n=71)**

<table>
<thead>
<tr>
<th>Response</th>
<th>ORR¹</th>
<th>95% CI</th>
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<td>12.7%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>29.6%</td>
<td>(24.9, 35.4)</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

**Updated efficacy analysis (n=103)**

<table>
<thead>
<tr>
<th>Response</th>
<th>ORR¹</th>
<th>95% CI</th>
<th>% of Patients Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>44.7%</td>
<td>(34.9, 54.8)</td>
<td>10.7%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>34.0%</td>
<td>(28.7, 40.2)</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

- In the primary analysis, the median duration of response was not reached with a median follow-up time of 14.1 months.¹
- The updated analysis showed a median duration of response of 34.7 months with a median follow-up of 20.4 months²

The efficacy of JEMPERLI was investigated in a global, multicenter, multiple cohort, open-label study of 71 patients with recurrent or advanced dMMR endometrial cancer who had progressed on or after treatment with a platinum-containing regimen. Patients received JEMPERLI 500 mg via intravenous infusion every 3 weeks for 4 doses followed by 1000 mg every 6 weeks until disease progression or unacceptable toxicity. An updated efficacy analysis for JEMPERLI included 103 patients using the same study criteria.¹

¹As measured from time of first response.¹
²Median follow-up time is a post hoc analysis of time since initial response.²

JEMPERLI has an established safety profile¹,²

- 4.8% of patients permanently discontinued treatment due to adverse reactions
- The most common adverse reactions (≥20%) were fatigue/asthenia, nausea, diarrhea, anemia, and constipation
- Safety data from the updated analysis were consistent with the established safety profile

**Complications of Allogeneic HSCT**

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after treatment with a PD-1/PD-L1–blocking antibody, which may occur despite intervening therapy. Monitor patients closely for transplant-related complications and intervene promptly.

**Embryo-Fetal Toxicity and Lactation**

- Based on its mechanism of action, JEMPERLI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after their last dose. Because of the potential for serious adverse reactions from JEMPERLI in a breastfed child, advise women not to breastfeed during treatment with JEMPERLI and for 4 months after their last dose.

**Common Adverse Reactions**

The most common adverse reactions (≥20%) in patients with dMMR EC were fatigue/asthenia, nausea, diarrhea, anemia, and constipation. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, decreased leukocytes, decreased albumin, increased creatinine, increased alkaline phosphatase, and increased alanineaminotransferase.

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

References:
1. JEMPERLI. Prescribing Information. GlaxoSmithKline; 2022.
2. Data on file, GlaxoSmithKline.
Brief Summary of Prescribing Information

JEMPERLI (dostarlimab-gxly) injection, for intravenous use

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

1 INDICATIONS AND USAGE
JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen [see Dosage and Administration (2.1) of full prescribing information].

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions
JEMPERLI is a monoclonal antibody that binds 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 inhibition of the immune response, potentially breaking peripheral tolerance, and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1-blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1-blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1-blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1-blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests 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.

Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information]. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (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 reaction is not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies, dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis
JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. 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 1.4% (7/515) of patients receiving JEMPERLI, including Grade 2 (1.2%) and Grade 3 (0.2%) pneumonitis. Pneumonitis led to discontinuation of JEMPERLI in 0.6% patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 86% of the 7 patients. Two patients reinstituted JEMPERLI after symptom improvement; of these, 1 patient had recurrence of pneumonitis.

Immune-Mediated Colitis

Immune-mediated colitis occurred in 1.4% (7/515) of patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Colitis led to discontinuation of JEMPERLI in 1 (0.2%) patient.

Systemic corticosteroids were required in 29% (27/7) of patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 3 patients in whom JEMPERLI was withheld for colitis, all reinstituted treatment with JEMPERLI.

Immune-Mediated Hepatitis
JEMPERLI can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 0.2% (1/515) of patients receiving JEMPERLI, which was Grade 3. Systemic corticosteroids were required and the event resolved.

Immune-Mediated Endocrinopathies
Adrenal Insufficiency: JEMPERLI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Adrenal insufficiency occurred in 1.4% (7/515) patients receiving JEMPERLI, including Grade 2 (0.8%) and Grade 3 (0.6%). Adrenal insufficiency resulted in discontinuation in 1 (0.2%) patient and resolved in 29% of the 7 patients.

Hypophysitis: JEMPERLI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypothyroidism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Thyroid Disorders: JEMPERLI can cause immune-mediated thyroid disorders. Thyrotoxicosis 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 JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Thyrotoxicosis: Thyrotoxicosis occurred in 0.4% (2/515) of patients receiving JEMPERLI; both were Grade 2. Neither event of thyrotoxicosis resolved; there were no discontinuations of JEMPERLI due to thyrotoxicosis.

Hypothyroidism: Hypothyroidism occurred in 7.2% (37/515) of patients receiving JEMPERLI, all of which were Grade 2. Hypothyroidism did not lead to discontinuation of JEMPERLI and resolved in 85% of the 37 patients. Systemic corticosteroids were not required for any of the 37 patients with hypothyroidism.

Hyperthyroidism: Hyperthyroidism occurred in 1.9% (10/515) of patients receiving JEMPERLI, including Grade 2 (1.7%) and Grade 3 (0.2%). Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 80% of the 10 patients. Systemic corticosteroids were not required for any of the 10 patients with hyperthyroidism.

Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis: JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Immune-Mediated Nephritis with Renal Dysfunction
JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis occurred in 0.4% (2/515) of patients receiving JEMPERLI; both were Grade 2. Nephritis did not lead to discontinuation of JEMPERLI and resolved in both patients. Systemic corticosteroids were required in 1 of the 2 patients experiencing nephritis.

Immune-Mediated Dermatologic Adverse Reactions
JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity [see Dosage and Administration (2.3) of full prescribing information].

Other Immune-Mediated Adverse Reactions
The following clinically significant immune-
mediated adverse reactions occurred in <1% of the 515 patients treated with JEMPERLI 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.

Nervous System: Meningitis, encephalitis, myelitis, and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuopathy.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Ocular: Uveitis, iritis, 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, including increases in serum amylase and lipase levels, gastritis, duodenitis.

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

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

5.2 Infusion-Related Reactions

Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions.

Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion if infusion-related reactions occur. JEMPERLI is based on severity of reaction [see Dosage and Administration (2.3) of full prescribing information].

5.3 Complications of Allogeneic HSC T

Fetal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (H SCT) 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 after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervention 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.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI 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:

• Severe and fatal immune-mediated adverse reactions [see Warnings and Precautions (5.1)]

• Infusion-related reactions [see Warnings and Precautions (5.2)]

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 JEMPERLI as a single-agent in 515 patients with advanced or recurrent solid tumors in the non-randomized, open-label, multicohort GARNET trial that enrolled 290 patients with endometrial cancer and 225 patients with other solid tumors. JEMPERLI was administered intravenously at doses of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until disease progression or unacceptable toxicity. Among the 515 patients, 42% were exposed for ≥24 weeks and 26% were exposed for ≥48 weeks.

Mismatch Repair Deficient (dMMR) Endometrial Cancer

The safety of JEMPERLI was evaluated in GARNET in 104 patients with advanced or recurrent dMMR EC who received at least 1 dose of JEMPERLI [see Clinical Studies (14.1) of full prescribing information]. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Among patients receiving JEMPERLI, 47% were exposed for 6 months or longer and 20% were exposed for >1 year.

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions in >2% of patients included sepsis (2.9%), acute kidney injury (2.9%), urinary tract infection (2.9%), abdominal pain (2.9%), and pyrexia (2.9%).

JEMPERLI was permanently discontinued due to adverse reactions in 5 (4.8%) patients, including increased transaminases, sepsis, bronchitis, and pneumonitis. Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in ≥1% of patients who received JEMPERLI were anaemia, diarrhea, increased lipase, and pyrexia. The most common adverse reactions (≥20%) were fatigue/asthenia, nausea, diarrhea, anaemia, and constipation.

The most common Grade 3 or 4 adverse reactions (≥2%) were anaemia and increased transaminases. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, decreased leucocytes, decreased albumin, increased creatinine, increased alkaline phosphatase and increased alanine aminotransferase.

Table 1 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR EC on JEMPERLI in GARNET.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades %</th>
<th>Grade 3 or 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and administration site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>1.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13</td>
<td>1.9</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03:

• Includes fatigue and asthenia.

• Includes anemia, decreased hemoglobin, iron deficiency, and iron deficiency anemia.

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

• Endocrine Disorders: Hypothyroidism, hyperthyroidism, hypophysitis.

• Eye Disorders: Iridocyclitis.

• Gastrointestinal Disorders: Colitis, acute pancreatitis.

• General Disorders and Administration Site Conditions: Pyrexia, chills.

• Renal and Urinary Disorders: Nephritis.

• Respiratory, Thoracic, and Mediastinal Disorders: Pneumonitis.

• Skin and Subcutaneous Tissue Disorders: Rash, erythema, pemphigoid.

Table 2 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR EC on JEMPERLI in GARNET.
Continued from previous page

6.1 Clinical Trials Experience (cont)

Table 2. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR Endometrial Cancer Receiving JEMPERLI in GARNET

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>JEMPERLI (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades*</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>37</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>21</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>30</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>27</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>25</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>16</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>15</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>26</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>15</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>15</td>
</tr>
</tbody>
</table>

* Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

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 to dostarlimab-gxly in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of dostarlimab was evaluated in GARNET. Treatment-emergent anti-drug antibodies (ADAs) against dostarlimab-gxly were detected in 2.1% of 384 patients who received dostarlimab-gxly at the recommended dosage. Neutralizing antibodies were detected in 1% of patients. Because of the small number of patients who developed ADAs, the effect of immunogenicity on the efficacy and safety of dostarlimab-gxly is inconclusive.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) of full prescribing information]. There are no available data on the use of JEMPERLI in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, dostarlimab-gxly 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 JEMPERLI 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 JEMPERLI 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 dostarlimab-gxly may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary
There is no information regarding the presence of dostarlimab-gxly in human 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 and for 4 months after the last dose of JEMPERLI.

8.3 Females and Males of Reproductive Potential

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

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

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

8.4 Pediatric Use

The safety and efficacy of JEMPERLI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 515 patients treated with JEMPERLI, 51% were younger than 65 years, 37% were aged 65 through 75 years, and 12% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions
Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid or other treatment and interruption or discontinuation of JEMPERLI. These reactions may include:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1)].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see Warnings and Precautions (5.1)].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding [see Warnings and Precautions (5.1)].
- Immune-mediated endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus [see Warnings and Precautions (5.1)].
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see Warnings and Precautions (5.1)].
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe skin reactions, SJS, TEN, or DRESS [see Warnings and Precautions (5.1)].
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms [see Warnings and Precautions (5.1)].
  - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection [see Warnings and Precautions (5.1)].

Infusion-Related Reactions
Advising patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.2)].

Complications of Allogeneic HSCT
- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity
- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].
- Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose [see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].

Lactation
- Advise women not to breastfeed during treatment with JEMPERLI and for 4 months after the last dose [see Use in Specific Populations (8.2)].

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PROGRESSION-FREE SURVIVAL (PFS) rates at 4 years of follow-up continued to show a benefit for tivozanib (Fotivda) compared with sorafenib (Nexavar) in patients with relapsed/refractory renal cell carcinoma (RCC) who received 2 or 3 prior systemic regimens, according to results from an exploratory analysis of the phase 3 TIVO-3 trial (NCT02627963). These results were presented at the 2022 International Kidney Cancer Symposium (IKCS): North America.

The findings showed that as of the data cutoff of May 24, 2021, the PFS rates continued to favor tivozanib over sorafenib (HR, 0.624; 95% CI, 0.49-0.79). These data were comparable to the PFS benefit reported at the original data cutoff (HR, 0.672; 95% CI, 0.52-0.87).

Specifically, patients treated with tivozanib (n = 175) achieved an investigator-assessed, 36-month PFS rate of 12.3% compared with 2.4% for patients treated with sorafenib (n = 175). The 48-month PFS rate was 7.6% for patients treated with tivozanib vs 0% for those given sorafenib (FIGURE1).

“A clinically relevant proportion of patients were alive and progression free at 3 and 4 years after initiating tivozanib therapy compared with sorafenib. This difference was consistent across all clinical and demographic subgroups evaluated,” lead study author Michael B. Atkins, MD, deputy director of the Georgetown Lombardi Comprehensive Cancer Center and the Scholl Professor and vice chair of the Department of Medical Oncology at Georgetown University Medical Center, and colleagues wrote in the poster presentation.

In March 2021, the FDA approved tivozanib for patients with relapsed/refractory advanced RCC following 2 or more prior systemic therapies. The regulatory decision was based on previously reported findings from the TIVO-3 trial.

During the meeting, investigators presented investigator-assessed PFS and overall survival (OS) for the intent-to-treat population and prespecified subgroups.

TIVO-3 enrolled patients with advanced clear cell metastatic RCC who progressed on 2 or 3 prior systemic therapies, including at least 1 VEGF tyrosine kinase inhibitor. Patients were stratified based on the prior regimen they were treated with and their International Metastatic RCC Database Consortium (IMDC) prognostic score. They were randomly assigned 1:1 to receive 1.34 mg of oral tivozanib once daily for 3 weeks on and 1 week off per cycle or 400 mg of oral sorafenib twice daily continuously in a 4-week cycle.

Subgroups with at least a 15% increase in PFS rate at 3 years included IMDC favorable risk (17.1% and 0% for tivozanib and sorafenib, respectively), female (17.5% and not evaluable [NE]), ECOG performance status of 0 (16.0% and 3.2%), and at least 65 years of age (15.3% and NE). Moreover, the mature OS data revealed a nonsignificant trend favoring tivozanib that continued to emerge with longer follow-up data (HR, 0.89; 95% CI, 0.70-1.14).

“The rates of investigator-assessed, long-term PFS were higher with tivozanib compared with sorafenib at every time point evaluated. The odds of experiencing long-term PFS at 36 months with tivozanib were over 5 times higher than with sorafenib,” Atkins said.

REFERENCES
MPN Landscape Shifts From JAK Inhibitors to Combination of Novel Agents

By Jordyn Sava

an associate professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston, discussed agents in combination with ruxolitinib (Jakafi) being examined for MPNs.

**MPN Landscape in 2022**

There are currently very few treatment options for patients with polycythemia vera (PV) that can control hematocrit levels, reduce the need for phlebotomy, and lower the incidence of thrombosis.

In November 2021, the FDA approved ropegasinterferon alfa-2b-njft (Besremi) for the treatment of adults with PV. The monopegylated, long-acting interferon was greenlighted based on findings from the phase 3 PROUD-PV/CONTINUATION-PV clinical trials (NCT01949805; NCT02218047), whose data revealed that, compared with hydroxyurea (Hydrea), the agent had a high and durable hematological response in patients over 36 months.

There have also been FDA approvals in more rare diseases, such as for avapritinib (Ayvakit) in advanced systemic mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm, and mast cell leukemia, and for pemigatinib (Pemazyre) in the setting of relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with an *FGFR1* rearrangement.²

Undergoing evaluation is rusfertide (PTG-300), which has been investigated in several clinical trials of patients with PV, and was granted breakthrough therapy designation as a treatment option for PV in June 2021.

Two of these trials exploring rusfertide are the phase 2 studies REVIVE (NCT04057040) and PACIFIC (NCT04767802), which were placed on clinical hold by the FDA in September 2021 after the identification of a nonclinical finding in a 26-week rasH2 transgenic mouse model study showed benign and malignant subcutaneous skin tumors.

However, the hold was lifted in October 2021, and new safety and stopping rules were added to the study protocols for the protection of patients in ongoing trials. No other unexpected safety signals were reported during the review.

In the myelofibrosis (MF) space, there are also JAK inhibitors beyond ruxolitinib. For thrombocytopenic patients with intermediate- or high-risk MF, the FDA approved pacritinib (Vonjoy), a JAK2/IRAK1 inhibitor, in February 2022. Momeletinib is another JAK1/2 inhibitor in advanced clinical development for anemic and symptomatic patients with MF. This agent has demonstrated significant improvements in anemia measures, spleen size, and symptoms in the ongoing pivotal phase 3 MOMENTUM trial (NCT04173494). Experts remain hopeful that momeletinib may soon receive regulatory approval as a treatment for anemic patients with MF.
Ruxolitinib
Two phase 3 trials led to the approval of ruxolitinib: COMFORT-I (NCT00952289) and COMFORT-II (NCT00934544). COMFORT-I was a randomized study of ruxolitinib vs placebo, while COMFORT-II evaluated ruxolitinib vs the best available therapy. Most patients in COMFORT-II received hydroxyurea.3

Both trials revealed a favorable spleen response with ruxolitinib. In COMFORT-I, approximately 42% of patients had a response rate in the spleen (odds ratio, 134.4; 95% CI, 18.0-1004.9; P<.001). In COMFORT-II, 97% of patients had a decrease in spleen volume compared with 56% of patients who received best available therapy.

Regarding the survival benefit, with an additional 4 months of follow-up after the primary analysis, the median overall survival (OS) of the pooled data from both COMFORT trials revealed an extension of life of about a year and a half (5.3 years [95% CI, 4.7-not estimable] vs 3.8 years [95% CI, 3.2-4.6, respectively]; HR, 0.70; 95% CI, 0.54-0.91; P=.0065).

Three JAK inhibitors have been approved for patients with MF: ruxolitinib, fedratinib (Inrebic), and pacritinib (Vonjo), with ruxolitinib being the standard of care for many patients with MF since 2011.

“Life after ruxolitinib leads to reduced overall survival,” Pemmaraju said in his presentation. “Also, the only factor in this retrospective study that improved OS was the introduction of novel agents post ruxolitinib failure, rather than the standard conventional agents already available in your therapeutic armamentarium.”

This leads investigators to wonder whether they can begin to modify the disease earlier than what is currently being achieved with new intervention studies of JAK monotherapy.

Investigational Agents
Pelahresib (CP1-0610) is a BET inhibitor that downregulates the expression of genes that contribute to the heterogenous features of MF. According to preliminary data from arms 2 and 3 of the phase 1/2 MANIFEST trial (NCT02158858),4 ruxolitinib and pelabresib demonstrated durable responses beyond week 24 in patients with MF who experienced a suboptimal response to ruxolitinib and in those who were JAK inhibitor-naïve.

Data showed that 68% (95% CI, 57%-78%) of patients with JAK inhibitor-naïve MF (n = 84; arm 3) experienced a reduction in spleen volume of at least 35% (SVR35) at week 24 when given the combination of ruxolitinib and pelabresib. Fifty-six percent (95% CI, 45%-67%) of patients in this arm experienced a 50% or greater reduction in total symptom score (TSS) from baseline at week 24, resulting in a median TSS change of ~59% at this time point.

Twenty percent of patients in arm 2 (a total of 81 patients with MF who had previously experienced a suboptimal response to ruxolitinib) experienced SVR35 at week 24, which was seen in 17% of those who were transfusion-dependent (TD) and in 26% of those who were non-transfusion dependent (NTD). Thirty percent of patients achieved SVR35 at any time point.

A 25% or higher SVR from baseline by week 24 was noted in 27% of patients. The median SVR was ~18%. The addition of pelabresib to ruxolitinib positively affected symptoms in these patients as well. The TSS50 at week 24 was 37%; this rate was 36% in TD patients and 39% in NTD patients, with a median symptom burden reduction of ~47%.

LIMBER-313 (NCT04551066) is a phase 3, randomized, double-blind, placebo-controlled study of ruxolitinib plus parsacilib vs ruxolitinib plus placebo in patients with MF who are treatment naïve for JAK and PI3K inhibitors. A total of 440 patients are estimated to be randomized to group A (n = 220) and receiving ruxolitinib and parsacilib 5 mg every day and to group B (n = 220) and receiving ruxolitinib plus placebo.

Looking Ahead
The REFINE trial (NCT03222609) examining treatment with navitoclax, a novel oral inhibitor of BCL-2 and BCL-2, plus ruxolitinib has entered phase 3 testing.9

“Preclinical studies almost a decade ago now show promising activity either as a single agent or in combination with a JAK inhibitor, leading to not only an improvement in the disease burden, but also potentially overcoming acquired resistance to a JAK inhibitor alone,” Pemmaraju noted.

A total of 34 patients were treated in cohort 1a and received at least 1 dose of navitoclax (starting at 50 mg/day and escalating to 300 mg daily based on tolerability) plus ruxolitinib at patients’ current stable dose. Bone marrow fibrosis (BMF) was assessed locally, and variant allele frequency reduction of the driver gene, either JAK2 or CALR, was assessed centrally by next-generation sequencing in the blood, at baseline, and at 24 weeks.

Investigators measured efficacy using SVR35 from baseline at week 24 as the primary end point. At week 24, 9 patients (27%) had achieved the primary end point of SVR35. Across the entire duration of the study, 14 (41%) patients met SVR35. The median duration for achieved SVR35 was 13.8 months (95% CI, 8.2- not estimable).

The secondary end points were reduction in TSS50 from baseline at week 24, hemoglobin improvement, change in BMF grade, and safety.

At week 24, 6 of the 20 patients evaluable for TSS50 (30%) achieved the desired reduction of symptoms, and 41% achieved TSS50 at any time on study. BMF had improved from baseline by grade 1 or greater in 11 of 33 patients at any time on study. Among the 11 patients with improved BMF enrolled in the study, 7 improved by 1 grade and 4 by 2 grades. The other 22 patients (67%) had equal or worsened BMF grades, with 13 patients having grade 3 fibrosis at baseline.

All patients had at least 1 adverse event (AE), and 30 patients (88%) experienced grade 3 or higher AEs. The most common AEs of any grade were thrombocytopenia (88%), diarrhea (71%), fatigue (62%), and nausea (38%). The most common grade 3 or higher AEs were thrombocytopenia without clinically significant bleeding (56%), anemia (32%), and pneumonia (12%).

“As we think about these trials in 2022 and beyond, I’m amazed to tell you that we have 10 to 12 ongoing phase 3 studies. 2023 will be our best year yet, and I end on a note of hope and optimism for our patients and for our field as we move towards the theme of disease modification and improved overall survival,” concluded Pemmaraju. TT

REFERENCES

CONFERENCE COVERAGE

INTERNATIONAL CONGRESS ON MYELOPROLIFERATIVE NEOPLASMS

Targeted Therapies in Oncology
December 2022 | Targeted Therapies in Oncology 47
JAK INHIBITORS (JAKIS) have an undeniable role in first-line and second-line treatment of myeloproliferative neoplasms (MPNs). But after JAKis, promising novel mechanisms may be implemented to improve patient outcomes.1

During the 14th International Congress on Myeloproliferative Neoplasms, John O. Mascarenhas, MD, discussed 3 targeted therapies for patients with MPNs: navtemadlin (AMG 232), imetelstat (MYF3001), and bomedemstat (IMG-7289). Mascarenhas is a professor of medicine at the Icahn School of Medicine at Mount Sinai and director of the Center of Excellence for Blood Cancer and Myeloid Disorders at Mount Sinai Tisch Cancer Center, New York, New York.

Navtemadlin
Results from the phase 2 BOREAS study (NCT03662126) indicate that navtemadlin may have a disease-modifying effect in myelofibrosis (MF).2 “This is an MDM2 inhibitor; it belongs to a class of drugs that bind MDM2. MDM2 is upregulated in MPNs, and the MDM2 negatively regulates wild-type p53. If you interrupt that interaction, you turn on a p53 pathway that [causes] the downstream effects that lead to cell death and senescence,” explained Mascarenhas during his presentation.1

The study assessed 111 patients with relapsed or refractory MF of whom 108 had 1 or more driver mutations, and 75 had 1 or more mutations in a high molecular risk gene. Further, driver mutations in JAK2 were reported in 73% of patients, in CALR in 19%, and in MPL in 12%.

Navtemadlin demonstrated spleen responses that were associated with reductions of MPN driver mutation burden, decreased peripheral CD34-positive cell counts, improvements in bone marrow fibrosis scores, and reduction in TNFα. Results specifically showed that a best driver gene reduction of at least 20% was observed in 34% of the patients with mutations in driver genes and high molecular risk variant allele fraction (VAF) reductions. Twenty-nine percent of those patients showed a complete VAF reduction. The reduction in driver allele VAF at any time on study was significantly associated with systemic vascular resistance (SVR). Reportedly, at least 20% of patients had SVR responses vs less than 20% in driver VAfs (32% vs 5%, respectively; \( P = .0072 \)).

According to Mascarenhas, navtemadlin was introduced to the clinic after early data, and hematologists/oncologists have encountered serious toxicity, specifically gastrointestinal (GI) toxicity. Because of the safety/tolerability profile of navtemadlin, other agents in the same class may offer better results, explained Mascarenhas. One example is imetelstat, a telomerase inhibitor that has less GI toxicity.

Imetelstat
Imetelstat is a first-in-class telomerase inhibitor shown to be competitive compared with other drugs in its class. Because the telomerase enzyme

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<th>TABLE. OVERALL SURVIVAL FOR IMETELSTAT*</th>
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<tr>
<td><strong>4.7 MG/KG IMETELSTAT</strong> (n = 48)</td>
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<tr>
<td>Median OS, months (95% CI) 19.9 (17.1-NE)</td>
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<td>1-year OS rate, % (95% CI, %) 78.6 (63.9-87.9)</td>
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<td>2-year OS rate, % (95% CI, %) 41.8 (27.1-55.8)</td>
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<tr>
<td><strong>9.4 MG/KG IMETELSTAT</strong> (n = 59)</td>
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<td>Median OS, months (95% CI) 29.9 (22.8-NE)</td>
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<tr>
<td>1-year OS rate, % (95% CI, %) 84.0 (71.6-91.4)</td>
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<td>2-year OS rate, % (95% CI, %) 57.5 (43.2-69.5)</td>
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<td><strong>BONE MARROW FIBROSIS IMPROVEMENT</strong></td>
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<td>Median OS, months (95% CI) 31.6 (23.6-NE)</td>
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<td>1-year OS rate, % (95% CI, %) N/A</td>
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<td>2-year OS rate, % (95% CI, %) N/A</td>
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<td><strong>NO BONE MARROW FIBROSIS IMPROVEMENT</strong></td>
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<td>Median OS, months (95% CI) 24.6 (18.4-NE)</td>
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<td>2-year OS rate, % (95% CI, %) N/A</td>
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N/A, not available; NE, not evaluable; OS, overall survival.
is highly upregulated in cancerous progenitor cells, treatment with an agent like imetelstat can allow continued, uncontrolled proliferation, according to Mascarenhas.1

Research has shown that disease modification with a telomerase inhibitor can improve survival.2 According to Mascarenhas, such an agent leads to dose-dependent fibrosis improvement, and fibrosis improvement correlates with longer median overall survival (OS). Moreover, telomerase inhibition is associated with at least a 20% reduction in VAF, which can also prolong OS, Mascarenhas explained.1

In a phase 2 study (NCT02426086), imetelstat showed clinical benefit in symptom response rate in the refractory MF population. The safety profile of the agent at the dose level of 4.7 mg/kg every 3 weeks was acceptable in the poor-risk population.3

In the 107 patients treated with imetelstat in the study, the median OS was 29.9 months. There was a bone marrow fibrosis improvement noted in 40.5% of evaluable patients and VAF reduction of driver mutations in 40.5% of evaluable patients.78% had a reduction in spleen volume from baseline with a mean SVR of –4%, and 37% of 27 patients who were evaluable for SVR, had at least a 50% reduction. Among the 27 patients who were evaluable for SVR, 78% had a reduction in spleen volume from baseline with a mean SVR of –4%, and 37% of them showed at least 20% SVR.

Safety results showed that diarrhea and dysgeusia (28% each) were the most common nonhematologic AEs reported by patients in the study. Serious cases of thrombocytopenia were observed during the study. The results showed no new safety signals or dose-limiting toxicities related to bomedemstat. Further, there were no treatment-related deaths during the study.

“The future will include multiple [JAKi] niches. Combination therapy approaches [and] up-front and second-line therapy have been showing new and novel agents that can [be used] after a JAKi failure. I think our goal should focus on its survival benefits. We need to move on beyond slated symptoms and start improving survival in patients with this disease,” Mascarenhas concluded. TT

REFERENCES
Indication

POLIVY in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least 2 prior therapies.

Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Important Safety Information

Peripheral Neuropathy

POLIVY can cause peripheral neuropathy, including severe cases. Peripheral neuropathy occurs as early as the first cycle of treatment and is cumulative. POLIVY may exacerbate preexisting peripheral neuropathy.

In Study GO29365, of 173 patients treated with POLIVY, 40% reported new or worsening peripheral neuropathy, with a median time to onset of 2.1 months.

Monitor for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of POLIVY.

Infusion-Related Reactions

POLIVY can cause infusion-related reactions, including severe cases. Delayed infusion-related reactions as late as 24 hours after receiving POLIVY have occurred. With premedication, 7% of patients (42/573) in Study GO29365 reported infusion-related reactions after administration of POLIVY.

Administer an antihistamine and an antipyretic prior to the administration of POLIVY, and monitor patients closely throughout the infusion. If an infusion-related reaction occurs, slow or interrupt the infusion and institute appropriate medical management.

Myelosuppression

Treatment with POLIVY can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In patients treated with POLIVY plus bendamustine and a rituximab product (BR) (n=45), 42% received primary prophylaxis with granulocyte colony-stimulating factor. Cytopenias were the most common reason for treatment discontinuation (18% of all patients).

Monitor complete blood counts throughout treatment. Cytopenias may require a delay, dose reduction, or discontinuation of POLIVY. Consider prophylactic granulocyte colony-stimulating factor administration.

Serious and Opportunistic Infections

Fatal and/or serious infections, including opportunistic infections such as sepsis, pneumonia (including *Pneumocystis jiroveci* and other fungal pneumonia), herpesvirus infection, and cytomegalovirus infection have occurred in patients treated with POLIVY. Grade 3 or higher infections occurred in 32% (55/173) of patients treated with POLIVY. Infection-related deaths were reported in 2.9% of patients within 90 days of last treatment.

Closely monitor patients during treatment for signs of infection. Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported after treatment with POLIVY (0.6%, 1/173). Monitor for new or worsening neurological, cognitive, or behavioral changes. Hold POLIVY and any concomitant chemotherapy if PML is suspected, and permanently discontinue if the diagnosis is confirmed.

Tumor Lysis Syndrome (TLS)

POLIVY may cause TLS. Patients with high tumor burden and rapidly proliferating tumors may be at increased risk of TLS. Monitor closely and take appropriate measures, including TLS prophylaxis.
Twice the response and double the duration with POLIVY®+BR* vs BR

**CR rate at EOT**

- **POLIVY+BR**: 40% (n=16/40)
- **BR**: 18% (n=7/40)

63% of patients in the POLIVY+BR arm (n=25/40) achieved a BOR compared to 25% in the BR arm (n=10/40).

**DoR >12 months**

- **POLIVY+BR**: 48% (n=12/25)
- **BR**: 20% (n=2/10)

In patients achieving a BOR, 64% achieved a DoR of ≥6 months in the POLIVY+BR arm (n=16/25) compared to 30% in the BR arm (n=3/10).

**Study design:** Study GO29365 was a pivotal, phase II, open-label study in patients with previously treated, R/R DLBCL (N=80) who had received at least 1 prior regimen and were not candidates for autologous HSCT at study entry. Patients with Grade 2 or higher peripheral neuropathy, prior allogeneic HSCT, active central nervous system lymphoma, or transformed lymphoma were not included in the study. Patients were randomized 1:1 to receive either POLIVY+BR or BR for six 21-day cycles. The primary endpoint was CR at EOT as assessed by IRC.

**Dosing protocol in Study GO29365:** Following premedication with an antihistamine and an antipyretic, POLIVY was given by intravenous infusion at 1.8 mg/kg on Day 2 of cycle 1 and on Day 1 of cycles 2 to 6. Bendamustine was dosed at 90 mg/m² intravenously on Days 2 and 3 of cycle 1 and on Days 1 and 2 of cycles 2 to 6. A rituximab product was administered at a dose of 375 mg/m² intravenously on Day 1 of cycles 1 to 6. Each cycle was 21 days in length.

**Hepatotoxicity**

Serious cases of hepatotoxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with POLIVY.

Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level.

**Embryo-Fetal Toxicity**

Based on the mechanism of action and findings from animal studies, POLIVY can cause fetal harm when administered to a pregnant woman. When administered to rats, the small molecule component of POLIVY, monomethyl auristatin E, caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities, at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise female patients with female partners of reproductive potential to use effective contraception during treatment with POLIVY and for at least 5 months after the last dose. Advise male partners of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose. Advise male patients to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose.

**Lactation**

Advise women not to breastfeed during treatment with POLIVY and for at least 2 months after the last dose.

**The Most Common Adverse Reactions**

The most common adverse reactions (≥20%) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

In Study GO29365, fatal adverse reactions occurred in 7% of recipients of POLIVY plus bendamustine and a rituximab product (BR) (n=45) within 90 days of last treatment. Serious adverse reactions occurred in 64% of patients, most often from infection. Serious adverse reactions occurring in ≥5% of recipients of POLIVY plus BR included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%).

Safety was also evaluated in 173 adult patients with relapsed or refractory lymphoma who received POLIVY, bendamustine, and either a rituximab product or obinutuzumab in Study GO29365, including the 45 patients with DLBCL. Fatal adverse reactions occurred in 4.6% of recipients of POLIVY within 90 days of last treatment, with infection as a leading cause. Serious adverse reactions occurred in 60%, most often from infection. Adverse reactions occurring in ≥20% of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting. Infection-related adverse reactions occurring in ≥10% of patients included upper respiratory tract infection, febrile neutropenia, pneumonia, and herpetic virus infection.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see a brief summary of the Prescribing Information on the following pages.

BOR=best overall response; CD79b=cluster of differentiation 79b; CR=complete response; DLBCL=diffuse large B-cell lymphoma; DoR=duration of response; EOT=end of treatment; HSCT=hematopoietic stem cell transplantation; IRC=independent review committee; MMAE=monomethyl auristatin E; NOS=not otherwise specified; PR=partial response; R/R=relapsed or refractory.

**References:**

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POLIVY® (polatuzumab vedotin-piiq) for injection, for intravenous use

Initial U.S. Approval 2019

This is a brief summary of information about POLIVY. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

POLIVY in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.

Accelerated approval was granted for this indication based on complete response rate data (see Clinical Studies (14)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Periphera,l Peripheral Neuropathy

POLIVY can cause peripheral neuropathy, including severe cases. Peripheral neuropathy occurs as early as the first cycle of treatment and is a cumulative effect (see Adverse Reactions (6.1)). POLIVY may exacerbate pre-existing peripheral neuropathy.

In Study GO29366, 53% of patients treated with POLIVY, 40% reported new or worsening peripheral neuropathy, with a median time to onset of 2.1 months. The peripheral neuropathy was Grade 1 or 2 in 26% of cases. Grade 2 in 12%, and Grade 3 in 2.3%. Peripheral neuropathy resulted in POLIVY dose reduction in 2.6% of treated patients, dose delay in 1.2%, and permanent discontinuation in 0.3%. Sixty-five percent of patients reported improvement or resolution of peripheral neuropathy after a median of 3.1 months, with 46% reported complete resolution.

The peripheral neuropathy is predominantly sensory; however, motor and sensorimotor peripheral neuropathy also occur. Monitor for symptoms of peripheral neuropathy such as hypesthesis, hyperesthesia, paresthesia, dysesthesia, neuropsychic pain, burning sensation, weakness, or gait disturbances. Patients experiencing new or worsening peripheral neuropathy may require a dose, dose reduction, or discontinuation of POLIVY (see Dosage and Administration (2.2)).

5.2 Infusion-Related Reactions

POLIVY can cause infusion-related reactions, including severe cases. Delayed infusion-related reactions can last as long as 24 hours following POLIVY infusion (see Warnings and Precautions (5.1)). Before each subsequent treatment, patients should be premedicated with an antihistamine and antipyretic. POLIVY 1.8 mg/kg was administered intravenously on Day 1 of each cycle. Infusion-related reactions occurred in 39% of patients treated with POLIVY plus BR. In recipients of POLIVY plus BR, infusion-related reactions occurred in 43% of patients treated with POLIVY plus BR. POLIVY plus BR included palbociclib (16%), thalidomide (10%), and sevoflurane (3%). Recipients of POLIVY plus BR had a median of 4 cycles, with 36% receiving 6 cycles. Infusion-related reactions included dyspnea, hypotension, and urticaria. 6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in this section reflect exposure to POLIVY in Study GO29365, a multicenter clinical trial for adult patients with relapsed or refractory diffuse large B-cell lymphoma (see Clinical Studies (14)). In patients treated with POLIVY plus BR, the trial included a single-arm safety evaluation of POLIVY and a combination with bendamustine and a rituximab product (BR) (n = 6). Followed by an open-label randomization to POLIVY in combination with BR versus BR alone (n = 18 treated per arm).

Following pretreatment with an antihistamine and antipyretic, POLIVY 1.8 mg/kg was administered by intravenous infusion on Day 2 of Cycle 1 and on Days 1 of Cycles 2-4, with a cycle length of 21 days. Bendamustine 95 mg/m²/day was administered intravenously on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of Cycles 2-4. A rituximab product dose of 375 mg/m² was administered intravenously on Day 1 of each cycle. Infusion-related reactions occurring in 5% or more of patients were:

- Nausea (71%)
- Hypothyrinemia (67%)
- Neutropenia (25%)
- Neutropenic fever (22%)
- Hyperphosphatemia (21%)
- Hypocalcemia (19%)
- Diarrhea (18%)
- Pyrexia (15%)
- Neutropenic sepsis (14%)
- Phlebitis (12%)
- Hypoglycemia (9%) (see Warnings and Precautions (5.2)).

In recipients of POLIVY plus BR, the trial included a single-arm safety evaluation of POLIVY plus BR. In recipients of POLIVY plus BR, infusion-related reactions included: nausea (20%), hypothermia (17%), fever (15%), and sepsis (7%).

In recipients of POLIVY plus BR, adverse reactions led to dose reduction in 18%, dose interruption in 51%, and permanent discontinuation of all treatment in 31%. The most common adverse reactions leading to treatment discontinuation were thrombocytopenia and neutropenia.

Table 4 summaries commonly reported adverse reactions. In recipients of POLIVY plus BR, adverse reactions in >20% of patients included neutropenia, thrombocytopenia, anemia, periorbital edema, urticaria, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of this label: Peripheral Neuropathy (see Warnings and Precautions (5.1)), Infusion-Related Reactions (see Warnings and Precautions (5.2)), Multifocal Leukoencephalopathy (PML) (see Warnings and Precautions (5.5)), and Progressive Multifocal Leukoencephalopathy (PML) (see Warnings and Precautions (5.2)).

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in this section reflect exposure to POLIVY in Study GO29365, a multicenter clinical trial for adult patients with relapsed or refractory diffuse large B-cell lymphoma (see Clinical Studies (14)). In patients treated with POLIVY plus BR, the trial included a single-arm safety evaluation of POLIVY plus bendamustine and a rituximab product (n = 6). Followed by an open-label randomization to POLIVY in combination with BR versus BR alone (n = 18 treated per arm).

The table includes a combination of grouped and ungrouped terms. Events were graded using NCI Common Toxicity Criteria (CTC) Version 4.0. Adverse reactions included laboratory abnormalities that are new or worsening in grade or with worsening from baseline unknown.

<table>
<thead>
<tr>
<th>Adverse Reactions Occurring in &gt;10% of Patients with Relapsed or Refractory DLBCL and &gt;5% More in the POLIVY Plus Bendamustine and Rituximab Product Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
</tr>
<tr>
<td>FyBold</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Weight decreased</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
</tbody>
</table>
| **Table 4** includes a combination of grouped and ungrouped terms. Events were graded using NCI CTC version 4.0. In recipients of POLIVY plus BR, adverse reactions in >20% of patients included neutropenia, thrombocytopenia, anemia, periorbital edema, urticaria, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.**
POLIVY® (polatuzumab vedotin-piiq)

Safety was evaluated in 173 adult patients with relapsed or refractory lymphoma who received POLIVY, bendamustine, and either a rituximab product or obinutuzumab in Study 020295, including the 45 patients with DLBCL described above. In the expanded safety population, the median age was 66 years (range 27 – 86), 57% were male, 91% had an ECOG performance status of 0–1, and 36% had a history of peripheral neuropathy at baseline.

Fata adverse reactions occurred in 4% of recipients of POLIVY within 90 days of last treatment, with infection as a leading cause. Serious adverse reactions occurred in 60%, most often from infection.

Table 6 summarizes the most common adverse reactions in the expanded safety population. The overall safety profile was similar to that described above. Adverse reactions in ≥20% of patients were diarrhea, neuropenia, peripheral neuropathy, fatigue, fibrinogenopenia, pyrexia, decreased appetite, anemia, and vomiting. Infusion-related adverse reactions in ≥10% of patients included upper respiratory tract infection, hives, neuropenia, pneumonia, and pyrexia.

**Table 6 Most Common Adverse Reactions (≥20% Any Grade or ≥5% Grade 3 or Higher) in Recipients of POLIVY and Chemotherapy for Relapsed or Refractory Lymphoma**

| Adverse Reaction by Body System | POLIVY + Bendamustine | POLIVY + Obinutuzumab
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>All Grades, (%)</td>
<td>Grade 3 or Higher, (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Platelet neutropenia</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>40</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td><strong>Genitourinary Disorders</strong></td>
<td>27</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>2.9</td>
</tr>
<tr>
<td>Palpitations</td>
<td>20</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

In addition to a combination of grouped and ungrouped terms.

- Primary prophylaxis with granulocyte colony-stimulating factor was given to 46% of all patients.
- Other clinically relevant adverse reactions (<20% any grade) included General disorders: infusion-related reaction (7%), infection: upper respiratory tract infection (6%), lower respiratory tract infection (10%), herpes zoster infection (10%), pyrexia (10%), Respiratory, thoracic, and mediastinal disorders: hypoxia (10%), infections: weight decrease (10%), transaminase elevation (8%), lipase increase (5%), Muscle and skeletal disorders: arthralgia (7%), eye disorders: blurred vision (1.2%).

8.2 Lactation

**Risk Summary**

There is no information regarding the presence of polatuzumab vedotin-piiq in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed while receiving POLIVY and for at least 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

**Pregnancy Testing**

Verify pregnancy status in females of reproductive potential prior to initiating POLIVY [see Use in Specific Populations (8.8)].

**Contraception**

Females

POLIVY can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.8)]. Advise females of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the final dose [see Nonclinical Toxicology (13.3)].

Based on gerotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the final dose [see Nonclinical Toxicology (13.3)].

**Infertility**

Based on findings from animal studies, POLIVY may impair male fertility. The reversibility of this effect is unknown [see Nonclinical Toxicology (13.3)].

8.4 Pediatric Use

Among 173 patients treated with POLIVY in Study 020295, 95 (55%) were ≥65 years of age. Patients aged ≥65 had a numerically higher incidence of serious adverse reactions (14%) than patients aged <65 (53%). Clinical studies of POLIVY did not include sufficient numbers of patients aged ≥65 to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

Avoid the administration of POLIVY in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN). Patients with moderate or severe hepatic impairment are likely to have increased exposure to MMAE, which may increase the risk of adverse reactions. POLIVY has not been studied in patients with moderate or severe hepatic impairment (see Clinical Pharmacology (12.3) and Warnings and Precautions (5.4)). No adjustment in the starting dose is required when administering POLIVY to patients with mild hepatic impairment (bilirubin greater than ULN but less than or equal to 1.5 × ULN or AST greater than ULN).

**Release Date:** June 2019

POLIVY® (polatuzumab vedotin-piiq)

M-US-0000051102/06 11/20

Manufactured by: Genentech, Inc.

A Member of the Roche Group

Genentech, Inc. (04/2020)

South San Francisco, CA

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International Symposium on Melanoma and Other Cutaneous Malignancies®, sponsored by Physicians’ Education Resource (PER®), LLC, is hoping to convey to attendees.

“We’re not done refining immune checkpoint inhibitor combinations and there are novel approaches, including adoptive T-cell therapy, that are undergoing research and may be generalizable to solid tumors,” Hamid, chief, Translational Research and Immunotherapy Program, and director, Melanoma Therapeutics Program at The Angeles Clinic and Research Institute in Los Angeles, California, told Targeted Therapies in Oncology™ during an interview prior to the conference.

In melanoma, immunotherapy approaches and targeted therapies have blazed a trail that may extend to other solid tumors owing to the disease’s significant immunogenicity and response to therapy, Hamid said. “Although we see responses in monotherapy regimens for melanoma, it’s the novel combinations that might have a better response in solid tumors,” he noted. The hybrid conference on February 4, 2023, at the Marriott Dallas Las Colinas in Irving, Texas, will feature presentations on BRAF therapy and bringing adoptive cell therapy into the clinic. Attendees can look forward to separate discussions focusing on neoadjuvant therapy, adjuvant therapy, and surgical management of melanoma.

**BRAF-Mutant Melanoma**

As director of melanoma research at The Angeles Clinic and Research Institute, Hamid is tasked with designing and running early-phase clinical trials. “We have to adhere to scientific rigor, which means that all the staff must be prepared [and] we have to be willing to have every interaction, each step, and every measurement scrutinized and audited by the FDA,” he said.

The work by Hamid and many other investigators led to the emergence of new therapies; however, there arose a need to understand the proper sequence of treatment for patients with melanoma. In particular, patients whose tumors harbor BRAF-mutant melanoma required more treatment clarity.

In BRAF-mutant melanoma, the treatment sequence of nivolumab (Opdivo) in combination with ipilimumab (Yervoy), followed by a BRAF and MEK inhibitor, was determined to be the optimal sequencing, according to findings of the DREAMseq trial (NCT02224781).1 Prior to the study, there was no clear sequencing path for PD-1 and CTLA-4 therapies combined with BRAF/MEK inhibition because of a lack of data from prospective studies.

The phase 3 DREAMseq trial assessed 265 patients with advanced BRAF-mutant melanoma who were randomly assigned to receive either nivolumab/ipilimumab in arm A or dabrafenib (Tafinlar) plus trametinib (Mekinist) in arm B. In the third and fourth arms (C and D), patients received either dabrafenib/trametinib or nivolumab/ipilimumab, respectively.

In arms A and D, patients were administered nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks in 4 doses, followed by an intravenous (IV) infusion of nivolumab 240 mg every 2 weeks for up to 72 weeks. In arms B and C, patients were administered dabrafenib 150 mg
twice per day and trametinib 2 mg orally daily until progressive disease.

Results from step 1 showed that the 2-year overall survival (OS) rate was 71.8% (95% CI, 62.5%-79.1%) in arm A compared with 51.5% (95% CI, 41.7%-60.4%) in arm B, demonstrating a difference of 20.3% (95% CI, 2.6%-37.9%; log-rank \( P = .010\)). The median progression-free survival (PFS) observed in arm A was 11.8 months (range, 5.9-33.5 months) vs 8.3 months (range, 6.5-11.3 months) in arm B (log-rank \( P = .054\)).

The overall response rate (ORR) observed during step 1 in arm A was 46.0% (95% CI, 36.6%-55.6%) compared with 43.0% (33.8%-53.6%) in arm B (Fisher exact test \( P = .690\)).

Results were also reported from step 2 of the study. In arm C, the median PFS was 9.9 months (8.3-20.6) compared with 2.9 months (2.6-8.9) in arm D. The ORR observed with arm C was 47.8% (26.8%-69.4%) vs 29.6% (12.7%-47.2%) with arm D.

“To understand the role of sequencing and all the potential confounding factors is what makes the rigor of these trials so important,” Hamid said. “Perhaps the most rewarding nonpatient care issue, though, is the collaboration between a community of like-minded people with a singular focus,” he added.

Adoptive T-Cell Therapy

Looking ahead, Hamid thinks tumor-infiltrating lymphocytes (TILs) will play a key role in melanoma. The success observed with lifileucel in metastatic melanoma has been met with enthusiasm.2

A phase 2 open-label, single-arm study (NCT02360579) evaluated patients with advanced melanoma who had been previously treated with checkpoint inhibitors and BRAF with or without MEK-targeted agents. Sixty-six patients received a lifileucel infusion of 1 x 10^7 or greater TIL cells.

Investigators reported that the objective response rate was 36% (95% CI, 25%-49%), with 2 complete responses and 22 partial responses. The median DOR was not reached after a median follow-up of 18.7 months.

Other TIL products are undergoing active evaluation as well: ITIL-168 (DELTA-1; NCT05050006) and ATL001 (NCT03997474).1

REFERENCES


WITH A RICHER understanding of renal cell carcinoma (RCC) tumor biology and the addition of immune checkpoint inhibitors (ICIs) to the treatment landscape, the prognosis for many patients with metastatic disease has improved. Still, resistance to checkpoint inhibition is common and contributes to the poor 5-year survival rate of 10% in the metastatic RCC setting. Consequently, regimens combining 2 ICIs or an ICI plus a different class of agent have been developed, with some encouraging results. However, adding a second drug increases both the expense of the treatment regimen and the risk of adverse events, inspiring an ongoing search for biomarkers that predict response to ICIs in metastatic RCC. These biomarkers would aid in selecting among existing regimens for patients across lines of treatment. Several have been investigated, including polybromo 1 (PBRM1) mutations and T-cell immunoglobulin and mucin domain-3 (TIM3) expression, which have shown variable or unreliable results.

When Wenxin (Vincent) Xu, MD, an oncologist at the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts, spoke about biomarkers in RCC with Targeted Therapies in Oncology™, he began by differentiating between the prognostic, predictive, and treatment-specific uses of biomarkers, pointing out that sometimes there is an overlap. As far as what one might find when conducting an online search for biomarkers in RCC, he said, “you will get hundreds, and while they might be scientifically interesting, they’ll most likely never reach the point where a clinician needs to know about them.”

**Prognostic Tools**

In terms of clinically applicable prognostic tools, risk stratification using a validated risk model, either the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model or the Memorial Sloan Kettering Cancer Center (MSK) risk model, remains central to patient evaluation and treatment decision-making (see TABLE 1). Interestingly, a retrospective study found that disagreement between the 2 risk models was associated with worse patient prognosis when compared with model agreement.

“In 2022, risk stratification, either with the IMDC or the MSK criteria, is the most important thing that we can do for patients. For example, ipilimumab [Yervoy] plus nivolumab [Opdivo] in the first line is only approved for intermediate- to poor-risk patients. And that bears out the data where the response rates are lower for favorable-risk patients. Whereas the other combinations of tyrosine kinase inhibitors [TKIs] plus immunotherapy [IO], such as axitinib [Inlyta] plus pembrolizumab [Keytruda], cabozantinib [Cabometyx] plus nivolumab, or lenvatinib [Lenvima] plus

**TABLE. IMDC OR MSKCC RISK-BASED PREFERRED TREATMENTS FOR METASTATIC RCC**

<table>
<thead>
<tr>
<th>RCC TYPE AND RISK LEVEL</th>
<th>PREFERRED FIRST-LINE THERAPY</th>
<th>PREFERRED SUBSEQUENT LINES OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC, favorable risk</td>
<td>Axitinib + pembrolizumab, Cabozantinib + nivolumab, Lenvatinib + pembrolizumab</td>
<td>Cabozantinib, Lenvatinib + everolimus, Nivolumab</td>
</tr>
<tr>
<td>Clear cell RCC, poor to intermediate risk</td>
<td>Axitinib + pembrolizumab, Cabozantinib + nivolumab, Ipilimumab + nivolumab, Lenvatinib + pembrolizumab, Cabozantinib</td>
<td></td>
</tr>
<tr>
<td>Non-clear cell RCC Preferred regimens</td>
<td>Clinical trial, Cabozantinib, Sunitinib</td>
<td></td>
</tr>
</tbody>
</table>

IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; RCC, renal cell carcinoma.

*By Suzanne Morris, DVM, MWC*
Potential Biomarkers

What, in addition to risk models and sarcomatoid or rhabdoid pathology, can provide needed prognostic information for a patient? The next biomarker that I think we can still use as informational but has never become a required companion diagnostic test is PD-L1 [expression]. We know that, based on CheckMate 214 [NCT02231749] data, PD-L1 expression does suggest an enrichment of patients who will respond. It doesn’t mean that if they’re PD-L1 negative that they won’t—that’s the challenge. That can be due to biopsy bias, heterogeneity of kidney cancer, the antibody used, all those caveats that go into PD-L1 staining,” Beckermann told Targeted Therapies in Oncology.6

Expanding on that difficulty associated with immunohistochemical assessment of PD-L1 protein expression, Xu observed that “the signal is really inconsistent. PD-L1 [expression] has been associated with a higher chance of response in randomized trials. The association is weaker in other randomized trials, and patients who are negative for PD-L1 expression still seem to have significant benefit from immune checkpoint inhibition. So this is one of those biomarkers that probably has some signal, but the signal is very inconsistent and the signal is nowhere near strong enough to deny someone the benefit of PD-L1.” Next to IMDC, in terms of research and validation, “we have the most information on PD-L1 testing just because of the development of checkpoint inhibitors over the last 10 years. So that gets us to things that are really exciting now and going into the future,” Beckermann said.

Vanderbilt University Trial

Indeed, exciting research on potential biomarkers in the metastatic RCC space is ongoing. “I will say up front that I am biased because we just opened a biomarker design clinical trial,” Beckermann said.

“I think it’s an effort to start moving the field towards having a biomarker. Our trial is based on the IMmotion150 [NCT01984242] and IMmotion151 [NCT02420821] data that tested bevacizumab [Avastin] and atezolizumab [Tecentriq] and asked: Can we correlate biology and gene expression data with response to treatment? And we’re not the only ones—other studies have now gone on to look at similar gene expression patterns. In Europe, the BIONIKK trial [NCT02960906] was a prospective attempt at looking at gene expression and assigning treatment options based on gene expression signatures. So that was a great step in prospective validation and development of biomarkers,” said Beckermann.7,8

“We’re looking at if patients have an angiogenically driven tumor based on their gene expression vs having more of an immune-responsive biology. Those are things like T-effector function clusters that would be suggestive of responding to a checkpoint inhibitor,” Beckermann said.

“We’re assigning ipilimumab plus nivolumab to patients who have these immune-based clusters, and we’re assigning cabozantinib plus nivolumab for patients who have an angiogenically driven gene expression pattern. We hope to learn more about the biology driving the remaining gene expression patterns and use this biology to identify novel therapeutic options,” Beckermann said.

Other Potential Biomarkers

Other emerging biomarkers in RCC that Xu finds interesting include studies involving the gut microbiome.

“Several groups have published several very provocative papers looking at the gut microbiome of patients with kidney cancer showing that certain bacteria are associated with higher chance of response to immunotherapy. And there was a recent phase 1 trial [NCT03829111] that was published this year showing that when they added a gut microbiome product, CBN588, to patients who received ipilimumab plus nivolumab, patients who got [CBN588] had a higher response rate with a hazard ratio of 0.15 for progression-free survival. That was very provocative and shows that maybe we can intervene at the gut microbiome and it could be a predictive biomarker that’s also an intervention,” said Xu.9–12 In NCT03829111, progression-free survival was significantly longer in patients receiving nivolumab-ipilimumab with CBN588 than without (12.7 months vs 2.5 months, respectively; 95% CI, 0.05-0.47; P = .001) (see pages 36-37).

“There’s a lot of data on kidney cancer and PBRM1 [mutations], which [are] fairly common, and there were a couple of papers in Science 4 years ago as well as some other papers before [showing] that PBRM1 mutations seem to promote response to immunotherapy across trials. That’s another investigational biomarker that is still kind of in the works,” said Xu.13

There is also interest in finding peripheral blood biomarkers in RCC. However, Beckermann said, “kidney cancer doesn’t seem to have the same shedding rate that some of the other tumor types do, so that’s going to be a challenge. But as those methods are being developed, I’m hopeful that there might be a noninvasive, peripheral blood method of monitoring biology over time.” As a part of that effort, Xu and other researchers have begun exploring kidney injury molecule-1 (KIM1) as a potential plasma biomarker in the early RCC setting.14,15 Still others are studying circulating tumor cells with respect to the nuclear protein Ki-67 as a potential prognostic biomarker in RCC.16 The urgent need for predictive biomarkers in metastatic RCC may drive additional studies of biomarkers in combination therapeutic trials, which could help optimize personalized therapies for RCC.”

95% CI, 0.05-0.47; P = .001) (see pages 36-37)
References are available on TargetedOnc.com.
See the latest data for SARCLISA + Kd

Explore the full results of the IKEMA phase 3 trial at sarclisahcp.com

Kd=Kyprolis (carfilzomib) and dexamethasone