Emerging Therapies Expand Options in Lung Cancer

WITH BENJAMIN P. LEVY, MD

PEER EXCHANGE
Novel Therapies Reshape Approaches to Transplant-Associated Thrombotic Microangiopathy

Persistent Development of WEE1 Pathway Inhibitors Begins to Pay Off

EXPERTS PICK 2021 ASCO HIGHLIGHTS
Harold J. Burstein, MD, PhD, on BREAST CANCER
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Neeraj Agarwal, MD, on GU CANCERS
Shannon N. Westin, MD, MPH, on GYN CANCERS
Sagar Lonial, MD, on MULTIPLE MYELOMA
Edward S. Kim, MD, MBA, on LUNG CANCER

NEW DRUG SPOTLIGHT
Bhavana Pothuri, MD, on Dostarlimab-gxly in dMMR Endometrial Cancer

VIRGINIA COMMONWEALTH UNIVERSITY
MASSEY CANCER CENTER
Community-Based Programs Have the Power to Remove Clinical Trial Barriers
by Khalid Matin, MD, FACP
IN ER+/HER2- METASTATIC BREAST CANCER (mBC)

CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

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

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


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Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 70.
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.
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 18%. 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. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. 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%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
BLENREP
(belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

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**INDICATIONS AND USAGE**

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

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

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 163), 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 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), 89% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

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

**Monitoring and Patient Instruction**

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

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

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

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

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**5.2 BLENREP REMS**

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

Notable requirements of the BLENREP REMS include the following:

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

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

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**5.3 Thrombocytopenia**

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenia event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 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 Doseage and Administration (2.3) of full Prescribing Information].

**5.4 Infusion-Related Reactions**

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer predmedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

**5.5 Embryo-Fetal Toxicity**

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

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

**6 ADVERSE REACTIONS**

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

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

**6.1 Clinical Trials Experience**

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

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) of BLENREP. The cytotoxic component was not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and to induce major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**6.2 BLENREP REMS**

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

Notable requirements of the BLENREP REMS include the following:

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

Further information is available at www.BLENREPREMS.com and 1-855-209-9188.
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 (>3%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

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

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

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratopathy(^a)</td>
<td>71 (44)</td>
</tr>
<tr>
<td>Decreased visual acuity(^b)</td>
<td>53 (28)</td>
</tr>
<tr>
<td>Blurred vision(^b)</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Dry eyes(^b)</td>
<td>14 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<th>General disorders and administration site conditions</th>
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<tbody>
<tr>
<td>Pyrexia</td>
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<tr>
<td>Fatigue(^c)</td>
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<tr>
<th>Procedural complications</th>
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<tbody>
<tr>
<td>Infusion-related reactions(^d)</td>
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</tbody>
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<table>
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tr>
<td>Arthralgia</td>
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<td>Back pain</td>
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<tr>
<th>Metabolic and nutritional disorders</th>
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<tr>
<td>Decreased appetite</td>
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<table>
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<tr>
<th>Infections</th>
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<tbody>
<tr>
<td>Upper respiratory tract infection(^n)</td>
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</tbody>
</table>

\(^a\) Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.

\(^b\) Visual acuity changes were determined upon eye examination.

\(^c\) Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

\(^d\) Dry eyes included dry eye, ocular discomfort, and eye pruritus.

\(^n\) Fatigue included fatigue and asthenia.

\(^p\) Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

\(^e\) Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

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

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

**Investigations:** Albuminuria.

6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-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)].

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 63% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m² or end-stage renal disease [ESRD] with eGFR <15 mL/min/1.73 m²) or 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)].
A wave of novel therapies have transformed the targeted treatment landscape for patients with lung cancer. Benjamin P. Levy, MD, hopes to contextualize these approaches during the lung cancer tract of the 39th Annual CFS®: Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow® sponsored by Physicians’ Education Resource®, LLC (PER®). In our feature story, Levy, who is cochair of the meeting, discusses these agents and how the future of care will rely on understanding mechanisms of resistance.

From the Editor
Gaps Persist in Understanding the Fundamentals of Informed Consent
By Maurie Markman, MD

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Persistence Pays Off in Lung Cancer Research

**BREAKTHROUGHS IN RESEARCH ARE** only the tip of the iceberg in the development of therapies for patients with cancer. The translation of novel agents from the lab to routine use in community clinics can take years from the commencement of a study to marketing approval.

“It takes a lot longer to start these studies [for patients with] early-stage [disease], and we’ve seen that in breast and colon [cancer studies] it can take years and years to report out some of these outcomes,” said Edward S. Kim, MD, MBA, said in an interview with OncologyLive®’s editorial director, Gina Mauro during the 2021 edition of OncLive News Network®: On Location at the American Society of Clinical Oncology (ASCO) Annual Meeting.

“In lung cancer where we’ve had really no major changes up until recently, all of these studies had to start years ago, and so I credit the companies, the investigators, who were really thinking ahead and trying to take some shots on goal,” he said.

In the past year alone, results of these studies are finally starting to come to fruition as the targeted treatment landscape has experienced a boom in available agents for patients with non–small cell cancer (NSCLC) whose disease harbors genomic mutations. This month’s drug spotlight highlights one of these agents, amivantamab-vmjw (Rybrevant), a bispecific antibody directed against EGF and MET receptors, which was approved by the FDA in May. It is the first targeted therapy for patients with NSCLC with *EGFR* exon 20 mutations, which are present in approximately 2% to 3% of patients with NSCLC.

Discussions held around major medical meetings with leading experts such as those conducted ASCO 2021 are one way OncLive® endeavors to bring the latest news and developments to the clinic. Another is through meetings hosted by Physicians’ Education Resource® (PER®), which provide opportunities to gather with colleagues and fit these innovative approaches into existing treatment paradigms to optimize care.

As in-person meetings and events return, conferences such as the 39th Annual CFS®: Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow® allow colleagues to discuss the pivotal data in the context of community care. The annual meeting brings together more than 2000 health care professionals to distill the rapid changes influencing the standards of care across solid and hematologic malignancies.

Benjamin P. Levy, MD, a cochair of the meeting and feature interview of this month’s cover story, hopes to pose questions surrounding mechanisms of resistance for targeted therapies in lung cancer as well as the role of liquid biopsy in the diagnostic algorithm for lung cancer during the meeting. “When I started, most of the talks were devoted to either chemotherapy or immunotherapy. The subject matter now has rapidly expanded to encompass all the new targeted therapies or immunotherapy combinations that are either under clinical investigation or FDA approved.”

CFS® is scheduled to take place as a hybrid event November 3 to 5. For more information or to register, visit: gotoper.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder
CONNECT WITH PURPOSE

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Gaps Persist in Understanding the Fundamentals of Informed Consent

by MAURIE MARKMAN, MD

THIS HAS BEEN AN INTERESTING and complex year in the realm of clinical trials. The results of multiple COVID-19 studies provide a remarkably powerful testimony to support well-designed, well-conducted trials and highlight the importance of interpreted investigative studies in optimizing the health of our society. Within the hierarchy of clinical trials, phase 3 randomized studies remain the gold standard, though some argue that appropriately designed meta-analysis of multiple studies provides even more definitive and meaningful insight.

Despite the remarkable success associated with the monumental double-blind, placebo-controlled COVID-19 vaccine studies, there has been considerable criticism of investigative approaches that examined potential therapeutic strategies to treat or prevent complications of this infection. In fact, the results of an extensive review of the topic document a number of concerning features. The report cites the use of underpowered, inadequately designed and conducted randomized studies; investigators leveraging large but poorly understood databases believed by some to be sufficient to avoid randomization; and, finally, the publication of results in high-impact medical journals by internationally recognized academics of observational data employing dubious or perhaps, nonexistent population-based sources for which stunningly inadequate vetting was employed.1

EXECUTION GAPS LEAD TO MISSED OPPORTUNITIES

The advent of rapid online coverage of research that has not undergone peer review has enabled widespread reporting of observational research and clinical trial efforts, the stated conclusions of which may be grossly overstated or, frankly, wrong.

Further, consider that in early 2020, COVID-19 was rapidly spreading, affecting both the developed and the developing world. The unfortunate absence of widespread international cooperation in the design and conduct of pragmatic clinical trials to definitively answer simple yet critical questions (eg, quickly defining the benefits or lack thereof for hydroxychloroquine, dexamethasone, and immune serum from survivors of a COVID-19 infection to treat or prevent complications) must be seen as a lost opportunity. However, it should be noted that countries with more centralized public health and research infrastructures mounted impressive controlled clinical trials that helped define clinical efficacy.2,3 Consider just how much could have been rapidly learned if these efforts were conducted on an international rather than a national scale.

MISSING THE MARK ON INFORMED CONSENT

A recent report regarding the informed consent process for patients enrolled on COVID-19 vaccine trials adds another element of concern, one that is highly relevant for clinical studies in the cancer domain.4 Considering the highly experimental nature of the initial phase 3 trial efforts of these vaccine products, including lack of solid knowledge of both efficacy and toxicity, one would have anticipated and hoped for considerable clarity in the informed consent document required from all participants. This would include material written at a reading level appropriate for the majority of individuals being asked to participate in this essential societal effort.

Unfortunately, investigators reported that the informed consent forms for 4 of the phase 3 COVID-19 randomized studies examined fell short of what would be considered optimal.4 First, each document was excessively long requiring at least 30 minutes to read at a pace of 240 words a minute. Second, each document...
exceeded the reasonable standard of ninth-grade reading ability and was overall rated as "difficult."

Finally, because of the truly experimental nature of these vaccine products, a placebo-controlled study design was essential. In the opinion of this commentator, there can be no objectively valid objection to this decision for the initial study designs. However, considering the fact that, by definition, approximately half of the study population would not receive the active product, it is perhaps more than a little surprising that just 1 of the 4 consent forms specifically stated that "participants with the placebo group might receive vaccine." Further, the investigators noted, "the reference was oblique and failed to specify timeline or other details." 4

Can the points described here regarding future plans of study participants randomized to the placebo arms possibly be considered appropriate informed consent? Of course, at the time consent was obtained, it was unknown if the various vaccines would be demonstrated to be safe and effective. However, that was always a realistic possibility; otherwise, why conduct the study?

There is a widely held perspective among members of the academic research community that participation in a clinical trial is fundamentally different from clinical care, and the researcher’s obligations to a "research subject" differ from those of a physician providing care to an individual patient. If this argument is accepted, one might conclude that the COVID-19 vaccine trials were specifically designed to answer a scientifically important question rather than provide protection from this dangerous virus for individual participants. Further, carrying the argument to its logical conclusion, investigators would not have an obligation to participants in the placebo arm, assuming the trial had a favorable outcome. Their only responsibility would be to conduct an excellent trial and report the results, which would, hopefully, be relevant to future individuals or patients.

In striking contrast, if we acknowledge both the critically important scientific aims of the study and its potential effect on participants, a plan for future management of individuals randomized to placebo—assuming a positive outcome—is ethically mandated. For example, this might have prospectively included a decision to offer active vaccination to this group once the vaccine received FDA approval for noninvestigative use.

Finally, it must be noted that the experience with informed consent described is potentially relevant for cancer investigative efforts whenever it is deemed appropriate to include a placebo-controlled study arm.

REFERENCES

Pembrolizumab Wins and Loses Indications for SCC and Gastric Cancers

The label for pembrolizumab (Keytruda) has added an indication following the FDA’s approval of an expansion of the agent for patients with locally advanced cutaneous squamous cell carcinoma (SCC) that is not curable by surgery or radiation. The PD-L1 inhibitor also lost an indication for patients with select gastric cancers following the voluntary withdrawal of the accelerated approval indication by developer Merck.

The expansion for patients with advanced SCC now permits the use of pembrolizumab as a monotherapy treatment option. The decision was based on the second interim analysis of the phase 2 KEYNOTE-629 trial (NCT03284424), in which the anti-PD-1 agent induced an objective response rate of 50% (n = 54; 95% CI, 36%-64%), which included a 17% complete response rate and a 33% partial response rate in the cohort of patients with locally advanced disease.

The withdrawn indication was one that underwent review by the FDA’s Oncologic Drugs Advisory Committee earlier this year and includes those with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express a PD-L1 combined positive score of 1 or more and who have progressed on or after 2 or more previous lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and HER2-/-neu-targeted therapy.

The initial 2017 approval was based on data from cohort 1 of the phase 2 KEYNOTE-059 trial (NCT02335411) in which the agent elicited an objective response rate of 13.3% (n = 143; 95% CI, 8.2%-20.0%). The continued approval was contingent on data from the phase 3 second-line KEYNOTE-061 (NCT02370498) and frontline KEYNOTE-062 (NCT02494583) trials, both of which failed to meet their primary end points. In April, the FDA’s Oncologic Drugs Advisory Committee met to evaluate the third-line cancer indication; it voted 6 to 2 against maintaining the approval in this population.

Solution Arrives for Patients With Hypersensitivity to E coli-Derived Asparaginase Products

The FDA has approved asparaginase Erwinia chrysanthemi (recombinant)-ryn (Rylaze) as part of a chemotherapy regimen to treat pediatric and adult patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma who are allergic to the Escherichia coli-derived asparaginase products.

The approval is supported by a study of 102 patients who either had a hypersensitivity to E coli-derived asparaginases or experienced silent inactivation, results of which showed that the recommended dose of the agent provided the target level of asparaginase activity in 94% of patients. The recommended dosage is 25 mg/m² intramuscularly every 48 hours. Approximately 20% of patients are allergic to the standard E coli-derived asparaginase, 1 component of a chemotherapy regimen, and therefore require an alternative treatment.

Previously, the only other FDA-approved drug for patients who have these allergic reactions has been in a global shortage since 2016, the agency stated. Each year, ALL occurs in approximately 5700 patients; about half are children, in which ALL is the most common type of pediatric malignancy.

ODAC Postpones Recommendation of Retifanlimab for Advanced Anal Cancer

The FDA’s Oncologic Drugs Advisory Committee (ODAC), in a 13-to-4 vote, has delayed issuing a recommendation regarding the full approval of retifanlimab (INCMGA0012) for the treatment of patients with locally advanced or metastatic squamous carcinoma of the anal canal.

Retifanlimab is an investigational, humanized, proprietary anti-PD-1 monoclonal antibody. In January 2021, the FDA granted a priority review designation for the antibody for patients who had progressed on or were intolerant of platinum-based chemotherapy. The decision was based on data from the open-label, single-arm, multicenter, phase 2 POD1UM-202 trial (NCT03597295), which was initially presented at the European Society for Medical Oncology Virtual Annual Congress 2020. Among 94 evaluable patients, the objective response rate was 13.8% (95% CI, 7.6%-22.5%), with a 1.1% complete response rate and a 12.8% partial response rate. The median duration of response was 9.5 months.

Committee members stated it would be “premature” to make a decision based on the available data, saying the low objective response rate might not represent a reliable estimate of response nor be reasonably likely to predict clinical benefit of retifanlimab. Additionally, few patients with HIV-positive status (10%) and few patients who were members of racial minority groups (1 Black patient, 4 Hispanic or Latino patients) were enrolled in the trial, which increases the uncertainty of the true treatment effect.

Committee members said a regulatory decision should be delayed until results from a randomized clinical trial are available. The agent is being examined in combination with carboplatin and paclitaxel in patients with inoperable locally recurrent or metastatic squamous carcinoma of the anal canal in the phase 3 POD1UM-303/InterAACT 2 clinical trial (NCT04472429). The results are expected in late 2025.

Oral Paclitaxel/Encequidar Holds Course for Metastatic Breast Cancer

Athenex, Inc held a type A meeting with the FDA to discuss the deficiencies raised in the complete response letter issued in March 2021 for the new drug application for oral paclitaxel plus encequidar for treatment of patients with metastatic breast cancer. In the complete response letter, the FDA shared safety concerns with the treatment approach because more neutropenia-related effects had been observed in patients who received oral paclitaxel plus encequidar than in those who received intravenous paclitaxel. Additionally, the agency flagged a concern with the blinded independent review committee reconciliation and reread process that could have introduced unmeasured bias and influence on the review.

During the type A meeting, Athenex shared updated analyses, which included overall survival data in various patient subgroups, to offer a comprehensive summary of the risks and benefits of the regimen and offered to collect additional data that could be used to inform the design of a new study. The FDA was cited as “supportive and encouraged [Athenex] to continue development,” adding that a “well-designed” and “well-conducted” trial could potentially address the concerns raised in the letter. The company is working on establishing a design for the trial and will share it with the FDA in the fourth quarter of 2021.
Indication
VITRAKVI® (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

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 trials.

Important Safety Information

Neurotoxicity: Among the 176 patients who received VITRAKVI, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively. The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Please see additional Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information.
Hepatotoxicity:

Monitor liver tests, including ALT and AST, every 1-3 weeks during the first month of treatment, then every 2-3 months as clinically indicated, and at any time if symptoms suggestive of hepatotoxicity occur.

If severe hepatotoxicity occurs, discontinue VITRAKVI and resume at 50 mg twice daily if tolerated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dose when resumed.

Important Safety Information (continued)

Neurotoxicity (continued): Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dose when resumed.

Hepatotoxicity: Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

Embryo-Fetal Toxicity: VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise women of the potential risk to a fetus. Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

Most Common Adverse Reactions (≥20%): The most common adverse reactions (≥20%) were: increased AST (45%), increased ALT (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%).
Across solid tumors
VITRAKVI IS HIGHLY EFFECTIVE IN TRK FUSION CANCER

Powerful response across multiple tumor types (as assessed by a BIRC, N=55)

Select patients for treatment with VITRAKVI based on the presence of an NTRK gene fusion in tumor specimens. An FDA-approved test for NTRK gene fusion is not currently available.

Study design: 55 adult and pediatric patients with unresectable or metastatic solid tumors with an NTRK gene fusion were included for the pooled efficacy analysis across the multicenter, open-label, single-arm clinical studies: LOXO-TRK-14001, NAVIGATE, and SCOUT. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease.

Major efficacy outcome measures: ORR and DOR, as determined by a BIRC according to RECIST version 1.1.

Important Safety Information (continued)

Drug Interactions: Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John’s wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Lactation: Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

Please see Brief Summary of full Prescribing Information on the following page.
VITRAKVI® (larotrectinib) capsules, for oral use
VITRAKVI® (larotrectinib) oral solution
Initial U.S. Approval: 2018

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

1 INDICATIONS AND USAGE

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neurotoxicity

Among the 176 patients who received VITRAKVI, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively [see Adverse Reactions (6.1)]. The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Advise patients and caregivers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed [see Dosage and Administration (2.3)].

5.2 Hepatotoxicity

Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients [see Adverse Reactions (6.1)]. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed [see Dosage and Administration (2.3)].

5.3 Embryo-Fetal Toxicity

Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its effect on TRK signaling, VITRAKVI is contraindicated in women who are pregnant or planning to become pregnant. Advise women of reproductive potential to use effective methods of contraception during treatment and for 1 week after the final dose of VITRAKVI [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

- Neurotoxicity [see Warnings and Precautions (5.1)]
- Hepatotoxicity [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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Data in WARNINGS AND PRECAUTIONS and below reflects exposure to VITRAKVI in 176 patients, including 70 (40%) patients exposed for greater than 6 months and 35 (20%) patients exposed for greater than 1 year. VITRAKVI was studied in one adult dose-finding trial [LOXO-TRK-14001 (n = 70)], one pediatric dose-finding trial [SCOUT (n = 43)], and one single arm trial [NAVIGATE (n = 63)]. All patients had an unresectable or metastatic solid tumor and no satisfactory alternative treatment options or disease progression following treatment.

Across these 176 patients, the median age was 51 years (range: 28 days to 82 years); 25% were 18 years or younger; 52% were male, and 72% were White, 11% were Hispanic/Latino, 8% were Black, and 3% were Asian. The most common tumors in order of decreasing frequency were soft tissue sarcoma (16%), salivary gland (11%), lung (10%), thyroid (9%), colon (8%), infantile fibrosarcoma (8%), primary central nervous system (CNS) (7%), and melanoma (5%). NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Among 120 adult patients treated with VITRAKVI 100 mg orally twice daily and 66% of (18 years or younger) received VITRAKVI 100 mg/m² twice daily up to a maximum dose of 100 mg twice daily. The dose ranged from 30 mg daily to 200 mg twice daily in adults and 8.6 mg/m² twice daily to 12.0 mg/m² twice daily in pediatrics [see Pediatric Use (8.4)].

The most common adverse reactions (≥20%) in order of decreasing frequency were fatigue, nausea, dizziness, vomiting, anemia, increased AST, cough, increased ALT, constipation, and diarrhea.

The most common serious adverse reactions (≥2%) were pyrexia, diarrhea, sepsis, abdominal pain, dehydration, cellulitis, and vomiting. Grade 3 or 4 adverse reactions occurred in 51% of patients; adverse reactions leading to dose interruption or reduction occurred in 37% of patients and 13% permanently discontinued VITRAKVI for adverse reactions.

The most common adverse reactions (1-2% each) that resulted in discontinuation of VITRAKVI were brain edema, intestinal perforation, pericardial effusion, pleural effusion, small intestinal obstruction, dehydration, fatigue, increased ALT, increased AST, enterocutaneous fistula, increased amylose, increased liver transaminases, muscular weakness, abdominal pain, asthma, decreased appetite, dyspnea, hyponatremia, jaundice, syncope, vomiting, acute myeloid leukemia, and nausea.

The most common adverse reactions (≥3%) resulting in dose modification (interruption or reduction) were increased ALT (6%), increased AST (6%), and dizziness (3%). Most (82%) adverse reactions leading to dose modification occurred during the first three months of exposure.

Adverse reactions of VITRAKVI occurring in ≥10% of patients and laboratory abnormalities worsening from baseline in ≥5% of patients are summarized in Table 2 and Table 3, respectively.

### Table 2 Adverse Reactions Occurring in ≥10% of Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3-4</th>
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<tr>
<td>General</td>
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<tr>
<td>Fatigue</td>
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<td>Pyrexia</td>
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<tr>
<td>Nervous System</td>
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<td>Dizziness</td>
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<td>Respiratory, Thoracic, and Mediastinal</td>
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<td>Musculoskeletal and Connective Tissue</td>
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<td>Decreased appetite</td>
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</tbody>
</table>

*Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 170 to 174 patients.

### Table 3 Laboratory Abnormalities Occurring in ≥5% Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Hypereosinophilia</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 170 to 174 patients.

**NCI-CTCAE v 4.03**

[National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03]

**One Grade 4 adverse reaction of pyrexia.**
7  DRUG INTERACTIONS

7.1  Effects of Other Drugs on VITRAKVI

Strong CYP3A4 Inducers

Co-administration of VITRAKVI with a strong CYP3A4 inhibitor may increase larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If co-administration of strong CYP3A4 inhibitors cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Sensitive CYP3A4 Substrates

Co-administration of VITRAKVI with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with sensitive CYP3A4 substrates. If co-administration of these sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

8  USE IN SPECIFIC POPULATIONS

8.1  Pediatric Use

Risk Summary

Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.3)], VITRAKVI can cause embryofetal harm when administered to a pregnant woman. There are no available data on VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats caused embryonic deaths and malformations at postnatal day (PND) 7 and at twice-daily doses of 0.6, 6, and 22.5 mg/kg between PND 28 and 70. The dosing period was equivalent to human pediatric populations from newborn to adulthood. The doses of 2/6 mg/kg twice daily (approximately 0.7 times the human exposure [AUC] at the clinical dose of 100 mg twice daily) and 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily) were maternally toxic doses [up to 40 times the human exposure (AUC) at the clinical dose of 100 mg twice daily]. Larotrectinib was administered in a juvenile toxicity study in rats at twice daily doses of 0.2, 2, and 7.5 mg/kg from postnatal day (PND) 7 to 27 and at twice-daily doses of 0.6, 6, and 22.5 mg/kg between PND 28 and 70. The dosing period was equivalent to human pediatric populations from newborn to adulthood. The doses of 2/6 mg/kg twice daily (approximately 0.7 times the human exposure [AUC] at the clinical dose of 100 mg twice daily) and 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily) were maternally toxic doses [up to 40 times the human exposure (AUC) at the clinical dose of 100 mg twice daily].

The main findings were transient central nervous system-related signs including ataxia, gait abnormalities, tremor, and circling in both sexes. An increase in the number of errors in a maze swim test occurred in females at exposures of approximately 4 times the human exposure (AUC) at the clinical dose of 100 mg twice daily. Decreased growth and delays in sexual development occurred in the mid- and high-dose groups. Mating was normal in treated animals, but a reduction in pregnancy rate occurred at the high-dose of 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily).

8.2  Lactation

Risk Summary

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

8.3  Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

Advise female patients of reproductive potential to use effective contraception during treatment with VITRAKVI and for at least 1 week after the final dose.

Males

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

Infertility

Female

Based on histopathological findings in the reproductive tracts of female rats in a 1-month repeated-dose study, VITRAKVI may reduce fertility [see Nonclinical Toxicology (13.1)].

Males

Based on the potential for serious adverse reactions in breastfed children, advise females not to breastfeed during treatment with larotrectinib and for 1 week after the final dose.

8.4  Pediatric Use

The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in adult or pediatric patients 28 days and older [see Adverse Reactions (6.1), Clinical Studies (14)].

The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was evaluated in 44 pediatric patients who received VITRAKVI. Of these 44 patients, 27% were 1 month to < 2 years (n = 12), 43% were 2 years to < 12 years (n = 19), and 30% were 12 years to < 18 years (n = 13). 43% had metastatic disease and 57% had locally advanced disease; and 91% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common prior treatments were: sarcoma (20%), soft tissue sarcoma (20%), primary CNS tumors (20%), and thyroid cancer (9%). The median duration of exposure was 5.4 months (range: 9 days to 1.9 years).

Due to the small number of pediatric and adult patients, the single arm design of clinical studies of VITRAKVI, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to VITRAKVI are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients compared to adult patients were increased weight (11% vs. 2%) and neutropenia (20% vs. 2%). One of the 44 pediatric patients discontinued VITRAKVI due to an adverse reaction (Grade 3 increased ALT).

8.5  Geriatric Use

Of 176 patients in the overall safety population who received VITRAKVI, 22% of patients were ≥ 65 years of age and 5% of patients were ≥ 75 years of age. Clinical studies of VITRAKVI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6  Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh B). Larotrectinib clearance was reduced in subjects with moderate (Child-Pugh C) or severe (Child-Pugh D) hepatic impairment [see in the overall safety population who received VITRAKVI, 22% of patients were ≥ 65 years of age and 5% of patients were ≥ 75 years of age. Clinical stores of VITRAKVI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.7  Renal Impairment

No dose adjustment is recommended for patients with renal impairment of any severity [see Clinical Pharmacology (12.5)].

17  PATIENT COUNSELING INFORMATION

Advis patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Neurotoxicity

Advise patients to notify their healthcare provider if they experience new or worsening neurotoxicity. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions [see Warnings and Precautions (5.1)].

Hepatotoxicity

Advise patients that they will need to undergo laboratory tests to monitor liver function [see Warnings and Precautions (5.2)].

Embryo-Fetal Toxicity

Advis males and females of reproductive potential of the potential risk to a fetus [see Warnings and Precautions (5.3)]. Use in Specific Populations (8.1)].

Advis females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective contraception during the treatment with VITRAKVI and for at least 1 week after the final dose [see Use in Specific Populations (8.3)].

Advis males with female partners of reproductive potential to use effective contraception during treatment with VITRAKVI and for at least 1 week after the final dose [see Use in Specific Populations (8.3)].

Lactation

Advise women not to breastfeed during treatment with VITRAKVI and for 1 week following the final dose [see Use in Specific Populations (8.3)].

Advis females of reproductive potential that VITRAKVI may impair fertility [see Nonclinical Toxicology (13.1)].

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, grapefruit or grapefruit juice while taking VITRAKVI [see Drug Interactions (7.1, 7.2)].
**Dostarlimab Expands Options for dMMR Endometrial Cancer**

_**by KYLE DOHERTY**_

**PATIENTS WITH MISMATCH REPAIR–DEFICIENT** (dMMR) recurrent or advanced endometrial cancer gained an efficacious and safe treatment option with the addition of dostarlimab-gxly (Jemperli). The FDA granted accelerated approval to the agent in April. The novel therapy was approved specifically for adult patients with dMMR recurrent or advanced endometrial cancer that has progressed on or following a prior platinum-containing regimen.

Findings from a 71-patient dMMR endometrial cancer cohort of the phase 1 GARNET trial (NCT02715284) supported the decision. Results showed that the confirmed overall response rate (ORR) achieved with dostarlimab was 42.3% (95% CI, 30.6%-54.6%), with 12.7% of patients experiencing a complete response (CR). Notably, the median duration of response (DOR) was not reached (2.6-22.4+) and 93.3% of patients had DORs of at least 6 months.

In an interview with OncologyLive®, Bhavana Pothuri, MD, a professor in the Department of Obstetrics and Gynecology at NYU Grossman School of Medicine and director of Gynecologic Oncology Clinical Trials at NYU Langone Health in New York, New York, spoke to how the accelerated approval of dostarlimab opens the treatment landscape to include personalized options for patients with endometrial cancer as well as some safety concerns observed with the agent.

**Please provide an overview of the design and outcomes of the GARNET trial.**

The GARNET trial enrolled patients with recurrent endometrial cancer. They were patients who had progressed on a prior platinum-based chemotherapy. These were patients with recurrent or advanced disease that was measurable. Patients were enrolled to 2 parallel cohorts. Cohort A1 [included patients with] dMMR endometrial cancer. [Cohort] A2 [included patients with] mismatch repair–proficient endometrial cancer.

I recently presented an updated analysis at the Society of Gynecologic Oncology 2021 Virtual Annual Meeting on Women’s Cancer. That included a larger cohort than what was presented to the FDA for approval, but the results are very similar. In the dMMR cohort of 103 patients, [investigators] noted an ORR of 44.7%, and that’s the population that dostarlimab was approved for. These data actually represent the largest reported cohort of dMMR endometrial cancer treated with the checkpoint inhibitor, and the efficacy was quite good.

**Please describe the mechanism of action of dostarlimab.**

Dostarlimab is a humanized anti–PD-1 monoclonal antibody that competitively inhibits the PD-1 receptor and blocks the ligand binding of PD-L1 and PD-L2 and belongs to the class of agents known as checkpoint inhibitors.

**In terms of safety, what should clinicians know about dostarlimab?**

The data that we presented showed the therapy was well tolerated. However, there are some very significant immune-related adverse effects AEs] that do occur. It’s important to keep these immune-related AEs in mind, counsel patients prior to the start of therapy, identify them early, and promptly manage these AEs. These immune-mediated reactions can occur in any organ system or tissue.

The most important thing is monitoring closely for these by evaluating blood work, including liver enzymes, creatinine, and thyroid function, as well as querying patients about symptoms such as cough or shortness of breath, which could be a sign of pneumonitis, or diarrhea, which could be a sign of colitis.

It’s important to note that most of these immune-related events occur in less than 5% of patients. The more common AEs are fatigue, nausea, and anemia, which are tolerable AEs.

**How does this approval affect the treatment standards for patients with dMMR endometrial cancer?**

It’s important in terms of having agents for the treatment of advanced endometrial cancer because [patients with] advanced or recurrent endometrial cancer [represent] a true unmet need; we don’t have many other active therapies.

This is a real win for our patients with endometrial cancer. Additionally, [the approval is] important in terms of understanding that endometrial cancer is the most common gynecologic cancer in the United States. The incidence, as well as the mortality [rates associated with the disease], has been increasing because of a greater proportion of obesity, as well as an increase in the number of patients with high-risk histologic subtypes. Having new additional therapies is very important. This is an exciting advance for gynecologic cancer and especially endometrial cancer.

Another thing that’s important about these checkpoint inhibitors is the DOR. Over 90% of responders had a DOR that was greater than 6 months. Having a new therapy is important, but having one that’s effective, well tolerated, and has a long-lasting DOR is also key.

One final thing that’s important is that traditionally when [patients have] recurrent endometrial cancer, we usually think that it is incurable. With immunotherapy agents, such as dostarlimab, we are seeing some CRs. These responses need longer follow-up, but the fact that the DOR for some patients in the dMMR cohort had not been reached is a sign perhaps we could be curing some of these patients. There were approximately 11% of patients who had CRs with dostarlimab in the dMMR cohort. That’s another exciting and important point which will need longer follow-up to address.

**What does the future hold for dostarlimab?**

Dostarlimab is being evaluated in the frontline setting, with chemotherapy, paclitaxel, and carboplatin in a large randomized, placebo-controlled phase 3 trial [RUBY; NCT03981796]. That trial will serve as the confirmatory trial for this accelerated approval. We’re all eagerly awaiting that data to see whether we can change the frontline treatment paradigm of endometrial cancer even further.

**REFERENCES**

**PIVOTAL CLINICAL TRIAL**

GARNET (NCT02715284) was a phase 1, first-in-human, multicenter, open-label study of dostarlimab in patients with advanced solid tumors who have limited available treatment options. The efficacy population for this indication consisted of a cohort of 71 patients with dMMR recurrent or advanced endometrial cancer who had progressed on or after treatment with a platinum-containing regimen.

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>N = 71</th>
</tr>
</thead>
<tbody>
<tr>
<td>64 (39-80)</td>
<td></td>
</tr>
</tbody>
</table>

**Histology**

- 70.4% Endometrioid carcinoma type 1
- 5.6% Serous
- 2.8% Squamous carcinoma
- 2.8% Mixed
- 1.4% Undifferentiated
- 1.4% Other
- 1.4% Unknown

**Prior treatment**

- 90.1% Anticancer surgery
- 78.9% Anticancer radiotherapy
- 5.6% Prior bevacizumab use
- 57.7% Any prior adjuvant/neoadjuvant anticancer treatment

**Number of prior regimens**

- 11.3% 1
- 25.4% 2
- 59.2% 3 or ≥ 4

**Efficacy Results in the dMMR Population of the GARNET Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dostarlimab (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>42.3% (30.6%-54.6%)</td>
</tr>
<tr>
<td>CR</td>
<td>12.7%</td>
</tr>
<tr>
<td>PR</td>
<td>29.6%</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>NR (2.6-22.4+)</td>
</tr>
<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>93.3%</td>
</tr>
</tbody>
</table>

CR, complete response; dMMR, mismatch repair–deficient; DOR, duration of response; NR, not reached; ORR, overall response rate; PR, partial response.

**Commonly Reported Adverse Effects**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Dostarlimab (n = 104)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>48%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
</tr>
<tr>
<td>Anemia</td>
<td>24%</td>
</tr>
<tr>
<td>Constipation</td>
<td>20%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14%</td>
</tr>
</tbody>
</table>

**Serious adverse effects**

- Sepsis 2.9%
- Acute kidney injury 2.9%
- Urinary tract infection 2.9%
- Abdominal pain 2.9%
- Pyrexia 2.9%

*Safety was evaluated in 104 patients who had received at least 1 dose of dostarlimab.

**Mechanism of action:**

- Dostarlimab is a humanized monoclonal antibody of the IgG4 isotype that binds to the PD-1 receptor, preventing interaction with PD-L1 and PD-L2.

**Dose:**

- Administer as an intravenous infusion over 30 minutes
- Doses 1 to 4: 500 mg every 3 weeks
- Subsequent dosing beginning 3 weeks (dose 5 onward): 1000 mg every 6 weeks

**Company:** GlaxoSmithKline LLC

**WARNINGS AND PRECAUTIONS**

- Immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogenic hematopoietic stem cell transplantation after PD-1/PD-L1-blocking antibody
- Embryo-fetal toxicity

**REFERENCES**


**Dostarlimab-gxly (Jemperli) FDA approval—April 22, 2021**

FDA grants accelerated approval for the PD-1–blocking antibody for the treatment of adult patients with mismatch repair–deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following a prior platinum-containing regimen.

**How supplied:**

- 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

**Company:** GlaxoSmithKline LLC

**Dose:**

- Administer as an intravenous infusion over 30 minutes
- Doses 1 to 4: 500 mg every 3 weeks
- Subsequent dosing beginning 3 weeks (dose 5 onward): 1000 mg every 6 weeks

**Company:** GlaxoSmithKline LLC
Amivantamab Paves a New Treatment Path for Patients With EGFR Exon 20–Mutant NSCLC

**by Jackie Collins**

**Q** What adverse effects do clinicians need to be aware of when prescribing this drug?

The most common [adverse effect that was] seen was infusion reaction, which is fairly universal [among] patients. [Reactions to the initial infusion resulted in amivantamab] needing to be stopped, delayed, slowed down, and sometimes even resumed the next day. That happened with only the first dose, and then subsequently patients were tolerant. [Amivantamab] also has some class effects, such as rash, diarrhea, and other things that we would see with other EGFR-targeted therapies, but those were minimal. The most prominent was an initial infusion reaction.

**Q** How does this approval shift the treatment paradigm of EGFR-mutant NSCLC?

Prior to this, there was no targeted therapy approved for patients with NSCLC [with] an EGFR exon 20 alteration. Recently at [the 2021 American Society for Clinical Oncology Annual Meeting, investigators] presented [results of] a real-world study out of France that showed that patients with EGFR exon 20–altered NSCLC treated with conventional chemotherapies did just [as well as] as individuals without EGFR alterations, showing that there’s a gap in targeting this type of EGFR alteration.4 [Amivantamab will] hopefully start to fill that gap.

**Q** What was noteworthy about the efficacy data that led to this approval?

The overall response rate was quite impressive for a second-line drug. It was approximately 40% and the median duration of response was 11.1 months. The overall survival data are still not mature, but those are both encouraging, especially in the second-line setting.

**Q** Please explain amivantamab’s mechanism of action.

Amivantamab is a bispecific antibody; it has 2 heads to the antibody: One is against EGFR, and the other is against MET. It targets resistance mechanisms in EGFR alteration–positive NSCLC and also, in particular, EGFR exon 20 alterations in [patients with] NSCLC.

**REFERENCES**

Amivantamab-vnjw (Rybrevant) FDA approval—May 21, 2021

FDA grants accelerated approval to amivantamab-vnjw (Rybrevant) for the treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations that has progressed on or after platinum-based chemotherapy.

Mechanism of action:
- Amivantamab is a bispecific antibody targeting the extracellular domains of EGFR and MET, where it blocks ligand binding resulting in the disruption of EGFR and MET signaling. In models studying exon 20 insertion mutations, amivantamab contributed to the degradation of EGFR and MET.

How supplied:
- 350 mg/7 mL (50 mg/mL) solution in a single-dose vial

Dose:
- Administer as an intravenous infusion after dilution based on baseline body weight
  - Less than 80 kg: 1050 mg (3 vials)
  - Greater than or equal to 80 kg: 1400 mg (4 vials)
- Administer weekly for 4 weeks, then every 2 weeks thereafter
  - Initial dose: split infusion in week 1 on day 1 and day 2

Company: Janssen Biotech Inc

PIVOTAL CLINICAL TRIAL

CHRYSALIS (NCT02609776) was a multicenter, nonrandomized, open-label, multicohort clinical trial of patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations who had progressed on or after platinum-based chemotherapy.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Brain metastases at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 (42-84)</td>
<td>YES 22.2%</td>
</tr>
<tr>
<td>n = 81</td>
<td>NO 77.8%</td>
</tr>
</tbody>
</table>

ECOG performance status

- 0: 32.1%
- 1: 66.7%
- 2: 1.23%

Exon 20 insertion location

- Helical region 66.7%
- Near loop 9.9%
- Far loop 22.2%
- Not detected by ctDNA 1.2%

EDFICACY RESULTS IN THE CHRYSALIS TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior platinum-based chemotherapy treated (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>40% (29%-51%)</td>
</tr>
<tr>
<td>CR</td>
<td>3.7%</td>
</tr>
<tr>
<td>PR</td>
<td>36%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>11.1 (6.9-NE)</td>
</tr>
<tr>
<td>Patients with DOR ≥6 months</td>
<td>63%</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PR, partial response.

WARNINGS AND PRECAUTIONS

- Infusion-related reactions
- Interstitial lung disease/pneumonitis
- Dermatologic adverse reactions
- Ocular toxicity
- Embryo-fetal toxicity

COMMONLY REPORTED ADVERSE EFFECTS IN THE CHRYSALIS TRIAL

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Amivantamab (N = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Rash</td>
<td>84%</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>64%</td>
</tr>
<tr>
<td>Paronychia</td>
<td>50%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>47%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>37%</td>
</tr>
<tr>
<td>Nausea</td>
<td>36%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33%</td>
</tr>
<tr>
<td>Edema</td>
<td>27%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>26%</td>
</tr>
<tr>
<td>Cough</td>
<td>25%</td>
</tr>
<tr>
<td>Constipation</td>
<td>23%</td>
</tr>
</tbody>
</table>

PATIENTS WHO RECEIVED PRIOR IMMUNOTHERAPY: 46%

REFERENCES
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION. 1,2*

Approved across 5 indications spanning a wide range of multiple myeloma patients

INDICATIONS
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:
• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
• as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
Efficacy consistent with intravenous daratumumab

- **DARZALEX FASPRO**™ demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients:
  - ORR was 41% (95% CI: 35%, 47%) for **DARZALEX FASPRO**™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259).
  - Eligible patients were required to have relapsed or refractory multiple myeloma who had received 3 or prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent.

- In a single arm of a multicohort, open-label trial, **DARZALEX FASPRO**™ with lenalidomide and dexamethasone (Drd) was evaluated in 65 patients with multiple myeloma who had received ≥2 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%).

- In a single arm of a multicohort, open-label trial, **DARZALEX FASPRO**™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%).

Fewer systemic ARRs vs intravenous daratumumab

- Nearly 3x reduction in systemic administration-related reactions (ARRs) with **DARZALEX FASPRO**™ vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on **DARZALEX FASPRO**™ had a systemic ARR of any grade vs 34% with intravenous daratumumab).
- Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with **DARZALEX FASPRO**™. See Important Safety Information for more details.

*For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.

In clinical trials of **DARZALEX FASPRO**™, **DARZALEX** (daratumumab), and the Prescribing Information for **DARZALEX®**, the term “inflation reactions” was used instead of “systemic administration-related reactions.”

Neutropenia

Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding **DARZALEX FASPRO**™ until recovery of neutrophils. In lower body weight patients receiving **DARZALEX FASPRO**™, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding **DARZALEX FASPRO**™ until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, **DARZALEX FASPRO**™ can cause fetal harm when administered to a pregnant woman. **DARZALEX FASPRO**™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with **DARZALEX FASPRO**™ and for 3 months after the last dose.

The combination of **DARZALEX FASPRO**™ with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received **DARZALEX FASPRO**™. Type and screen patients prior to starting **DARZALEX FASPRO**™.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some **DARZALEX FASPRO**™-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The most common adverse reaction (≥20%) with **DARZALEX FASPRO**™ monotherapy is: upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematologic laboratory abnormalities (≥40%) with **DARZALEX FASPRO**™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.
Neutropenia occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting injection-site reaction was injection site erythema. These local reactions of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) were observed.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.8%, Grade 2: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetylmethionine and corticosteroids [see Dosage and Administration (2.3) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction [see Adverse Reactions]. Daratumumab is a human IgG kappa monoclonal antibody that can be detected in plasma and screen patients prior to starting DARZALEX FASPRO and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO [see Dosage and Administration (2.1) in Full Prescribing Information].

Monitor complete blood cell counts periodically during treatment according to the formulation [see Warnings and Precautions and Adverse Reactions].

Daratumumab may increase thrombocytopenia induced by background therapy. Consider withholding DARZALEX FASPRO until recovery of neutrophils. Lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Adverse reactions requiring dosage interruptions in >5% of patients were:
- Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
- Neutropenia [see Warning and Precautions].
- Thrombocytopenia [see Warning and Precautions].

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

In Combination with Bortezomib, Melphalan and Prednisone
The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from week 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 8 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fetal adverse reactions occurred in 3.0% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient was neutropenic sepsis.

Dose adjustments (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (>20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Infections

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

CONTRAINDICATIONS
DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation [see Warnings and Precautions and Adverse Reactions].

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO.

Pre-medicate patients with histamine-1 receptor antagonist, acetylmethionine and corticosteroids [see Dosage and Administration (2.3) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction [see Adverse Reactions].

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antitubulin test (Direct Combs test). Daratumumab-mediated positive indirect antitubulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [see References]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions].

In rare instances, transfusion centers of this interference with serological testing and informed blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO [see Dosage and Administration (2.1) in Full Prescribing Information].

Infections

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>
Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) and lenalidomide and dexamethasone (D-Rd) include:

- **Fatigue:**
  - D-VMP: 36%
  - D-Rd: 52%

- **Diarrhea:**
  - D-VMP: 33%
  - D-Rd: 96%

- **Vomiting:**
  - D-VMP: 21%
  - D-Rd: 93%

- **Abdominal pain:**
  - D-VMP: 13%
  - D-Rd: 88%

- **Pneumonia:**
  - D-VMP: 22%
  - D-Rd: 14%

General disorders and administration site conditions:

- **Fatigue:**
  - D-VMP: 36%
  - D-Rd: 52%

- **Edema peripheral:**
  - D-VMP: 34%
  - D-Rd: 14%

Nervous system disorders:

- **Cough:**
  - D-VMP: 24%
  - D-Rd: 20%

Table 1: Select Hematology Laboratory Abnormalities Worsening from DARZALEX FASPRO™

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisonea (%)</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>All Grades 96</td>
<td>Grades 3-4 (%) 52</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>All Grades 93</td>
<td>Grades 3-4 (%) 84</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>All Grades 93</td>
<td>Grades 3-4 (%) 42</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>All Grades 88</td>
<td>Grades 3-4 (%) 49</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>All Grades 48</td>
<td>Grades 3-4 (%) 19</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-VMP (N=67).

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO.

Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3%</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders:

- **Diarrhea:**
  - All Grades: 45%
  - Grades ≥3: 5%

- **Hypertension:**
  - All Grades: 13%

- **Hypotension:**
  - All Grades: 10%

- **Skin and subcutaneous tissue disorders:**
  - Rash: 13%

Vascular disorders:

- **Hypertension:**
  - All Grades: 13%

- **Hypotension:**
  - All Grades: 10%

Nervous system disorders:

- **Cough:**
  - All Grades: 14%

Psychiatric disorders:

- **Insomnia:**
  - All Grades: 17%

Infections:

- **Upper respiratory tract infection:**
  - All Grades: 43%

Musculoskeletal and connective tissue disorders:

- **Musculoskeletal chest pain:**
  - All Grades: 12%

Cardiac disorders:

- **Atrial fibrillation:**
  - All Grades: 12%

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) include:

- **Fatigue:**
  - All Grades: 96%
- **Diarrhea:**
  - All Grades: 93%
- **Vomiting:**
  - All Grades: 93%
- **Abdominal pain:**
  - All Grades: 88%
- **Pneumonia:**
  - All Grades: 48%

Denominator is based on the safety population treated with D-VMP (N=67).
**DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection**

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** upper respiratory tract infection, nasopharyngitis
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

### Table 4: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO or Intravenous Daratumumab

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>8</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>96</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with D-Rd (N=65).

**Monotherapy**

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials [142] in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously at daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 2% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

Table 5 summarizes the adverse reactions in COLUMBA.

### Table 5: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO&lt;sup&gt;b&lt;/sup&gt; (N=296)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Intravenous Daratumumab&lt;sup&gt;b&lt;/sup&gt; (N=258)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24</td>
<td>1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>22</td>
<td></td>
<td>21</td>
<td>1&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td></td>
<td>8</td>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11</td>
<td></td>
<td>10</td>
<td>0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11</td>
<td></td>
<td>0.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16</td>
<td></td>
<td>16</td>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infusion reactions&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13</td>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>34</td>
<td></td>
<td>34</td>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td></td>
<td>13</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Chills</td>
<td>6</td>
<td>0.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>12</td>
<td></td>
<td>12</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Back pain</td>
<td>10</td>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>12</td>
<td></td>
<td>12</td>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>14</td>
<td></td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11</td>
<td></td>
<td>11</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with D-Rd (N=65).

**Immuneologic**

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

Treatment-emergent anti-daratumumab antibodies were tested in 451 patients treated with DARZALEX FASPRO as monotherapy or as part of a combination therapy. One patient (0.2%) who received DARZALEX FASPRO tested positive for anti-daratumumab antibodies and transient neutralizing antibodies. However, the incidence of antibody development might not have been reliably determined because the assays that were used have limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab.

Treatment-emergent anti-rHuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (16/192) of patients who received DARZALEX FASPRO as part of combination therapy. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposures. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

**Postmarketing Experience**

The following adverse reactions have been identified with use of intravenous daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Immune System:** Anaphylactic reaction

**Gastrointestinal:** Pancreatitis
Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with diethanolamine (DEA) to disrupt daratumumab binding [see References] or genotyping. Since the Kell blood group system is also sensitive to DEA treatment, supply K-negative units after ruling out or identifying alloantibodies using DEA-treated RBCs.

Animal Data

Mice that were genetically modified to eliminate all CD38 recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral embryonic development (frogs).

Fetal/Neonatal Adverse Reactions

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (134 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

Darzalex Faspro™ can cause fetal harm when administered to a pregnant woman. The association of adverse events with daratumumab use is based on the mechanism of action and data from target antigen CD38 knockout animal models [see Data]. There are no available data on the use of Darzalex Faspro™ in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and 15% to 20%, respectively. The combination of Darzalex Faspro™ and lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Lenalidomide is only available through a REMS program. Refer to the lenalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunglobulin G1 (IgG1) monoclonal antibodies are transfed across the placenta. Based on its mechanism of action, Darzalex Faspro™ may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematologic evaluation is completed.

Data

Animal Data

Darzalex Faspro™ for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when Darzalex Faspro™ is administered with lenalidomide and dexamethasone, advise women not to breastfeed during DARZALEX FASPRO treatment. Refer to lenalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

Darzalex Faspro™ can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Embryo-Fetal Toxicity

Advisse pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Darzalex Faspro™ and for at least 3 months after the last dose. Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

Advisse patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see Warnings and Precautions].

Product of Switzerland

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INTERACTIVE NEWS

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TOP TWEETS

When used in patients with R/R DLBCL who are not candidates for stem cell transplantation, the next-generation CD37-directed radioimmunotherapy 177Lu liliotomab satetraxten showcased early clinical activity w/ favorable tolerability. #lymsm

@SidpadiaIR, MD, of @UCLAHealth explains TheraSphere’s unique mechanism of action and what its approval means in HCC and beyond

Cita-cel induced an overall response rate of 97.9% with an 80.4% rate of stringent complete response, at a median follow-up of 18 months. @szusmani @LevineCancer @ASCO #ASCO21 #mmsm

@NataliyaUboha, MD, PhD, of @UWCarbone discusses pivotal research efforts made in gastric and pancreatic cancers and highlighted the next steps for novel approaches.

Florida Cancer Specialists Move Toward Full Integration of In-House Genomic Testing @LucioGordanMD @FLCancerFound #precisionmedicine #genomics

ONCLIVE ONAIR™ PODCAST SPOTLIGHT

FDA APPROVAL INSIGHTS TIVOZANIB IN R/R ADVANCED RCC

Brian I. Rini, MD, discusses the FDA approval of tivozanib (Fotivda) for the treatment of adult patients with relapsed/refractory (R/R) advanced renal cell carcinoma (RCC) following 2 or more prior systemic therapies. Rini explains the unique elements of the TIVO-3 trial (NCT02627963) and potential next steps for research.

LISTEN: bit.ly/3xa1Wub

FDA APPROVAL INSIGHTS IDE-CEL FOR R/R MM

Nikhil C. Munshi, MD, speaks on the significance of the FDA approval of idecabtagene vicleucel (ide-cel; Abecma) as the first BCMA-directed chimeric antigen receptor (CAR) T-cell therapy for patients with relapsed/refractory multiple myeloma (R/R MM) including data from the KarMMa trial (NCT03361748), which served as the basis for the approval, and next steps for CAR T-cell therapy in the field.

LISTEN: bit.ly/3drNwhn

ONCLIVE ON AIR™

PANT PROJECTS AN EXPANDING ROLE FOR TARGETED THERAPY IN PANCREATIC CANCER

Shubham Pant, MD, provides an overview of PARP inhibitors, KRAS inhibitors, and other targeted agents for patients with pancreatic cancer, discusses the germline and somatic testing methods for these drugs, and shares his hope for the future of drug development in the field.

LISTEN: bit.ly/3h745Bs

RESEARCH REFLECTIONS

PATEL PREVIEWS COLLABORATIVE RESEARCH PROGRAM WITH SD-101 IN GASTRIC CANCERS

Sapna Patel, MD, discusses the strategic research collaboration between The University of Texas MD Anderson Cancer Center and TriSalus Life Sciences to evaluate SD-101, an investigational toll-like receptor 9 (TLR9) agonist, in combination with checkpoint inhibitors for the treatment of patients with pancreatic cancer and hepatocellular carcinoma.

LISTEN: bit.ly/36fFHaB

SPOTLIGHT

COLEMAN CENTERS THE DISCUSSION ON PRACTICE-AFFIRMING ASCO TRIALS IN GYNECOLOGIC ONCOLOGY

Practice-validating trials in cervical cancer, endometrial cancer, and ovarian cancer were the focus of the gynecologic oncology session at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting, explained Robert L. Coleman, MD. Coleman is the chief scientific officer of The US Oncology Network and the 2020 Giants of Cancer Care® winner in Gynecologic Oncology. New data from each histology carries relevant implications on extended therapy, surveillance, and biomarker testing.

Coleman covered a wide range of studies, including maintenance therapy with the autologous vaccine, gemogenovatucel-T (Vigil) in the phase 2b VITAL trial (NCT02346747), intensive surveillance strategies in endometrial cancer in the TOTEM trial (NCT00916708), and the results of chemoradiation strategies for women with cervical cancer in the phase 3 OUTBACK study (NCT01414608).

READ MORE: bit.ly/3AeWvvM

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JOURNAL SPOTLIGHT

GENOMIC CANCER PROFILING: SETTING A NEW STANDARD IN LUNG CANCER TREATMENT
by Martin Dietrich, MD, PhD
Genomic profiling has revolutionized the way cancer care is being approached. With the breadth of targetable mutations, next-generation sequencing provides a highly sensitive, parallel approach to identifying the complete set of relevant biomarkers to guide therapy, allowing clinicians to match biology with the appropriate therapy and refining the one-size-fits-all approaches.

READ MORE: bit.ly/365WBbe

ONCLIVE® VIDEOS

JONES ON THE IMPORTANCE OF TESTING FOR MICROSATellite INSTABILITY IN CRC
Jeremy C. Jones, MD, hematologist/oncologist, at the Mayo Clinic in Jacksonville, Florida, discusses the importance of testing for microsatellite instability high (MSI-H) in colorectal cancer (CRC). Although MSI-H tumors account for approximately 5% of all CRC, this patient subgroup has demonstrated dramatic response rates with checkpoint inhibitor therapy, Jones explains. As such, it is critical to ensure patients with MSI-H CRC are appropriately identified and treated with checkpoint inhibitors, such as pembrolizumab (Keytruda), Jones adds.

WATCH: bit.ly/3jsk3rq

WANG ON THE POTENTIAL OF MENIN INHIBITORS IN AML
Eunice Wang, MD, the chief of the Leukemia Service at Roswell Park Comprehensive Cancer Center in Buffalo, New York, discusses the potential impact of menin inhibitors on the treatment of acute myeloid leukemia (AML). Menin inhibitors potentially represent the next of focal point of targeted treatment for patients with AML, joining other targeted therapies, such as the CD33-targeting antibody-drug conjugate gemtuzumab ozogamicin (Mylotarg), FLT3 inhibitors midostaurin (Rydapt) and gilteritinib (Xospata), and IDH inhibitors ivosidenib (Tibsovo) and enasidenib (Idhifa).

WATCH: bit.ly/3jFosr9

GHIA ON THE EFFICACY OF IBRUTINIB/VENETOCLAX IN CLL
Paolo Ghia, MD, PhD, a professor of medical oncology and the director of the Strategic Research Program on CLL and the B Cell Neoplasia Unit at Vita-Salute San Raffaele University in Milan, Italy, discusses results from the phase 3 GLOW trial (NCT03462719), which evaluated the combination of ibrutinib (Imbruvica) and venetoclax (Venclexta) as a first-line treatment for patients with chronic lymphocytic leukemia (CLL).

WATCH: bit.ly/2ToVNPP

READ MORE: bit.ly/3hkRmK1

NOTABLE QUOTABLES

“Sometimes [geriatric assessment] doesn’t generate interest from the community because it doesn’t sound as exciting as drug development or immunotherapy. However, we know it improves outcomes.”

—Melissa (Kah Poh) Loh, BMedSci, MBBCh, BAO
University of Rochester Medical Center
Rochester, New York

“This is an exciting time; immunotherapy has reshaped liver cancer treatment... There is a strong rationale to incorporate immunotherapies earlier on in the treatment process.”

—Parissa Tabrizian, MD, MSc
Icahn School of Medicine at Mount Sinai
New York, New York
UNSILENCE AN EXPRESSION INSTRUMENT

When is TAZVERIK® (tazemetostat) appropriate for your relapsed or refractory (R/R) follicular lymphoma (FL) patient?

Important Safety Information

Warnings and Precautions

• Secondary Malignancies
  The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

• Embryo-Fetal Toxicity
  Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

TAZVERIK is indicated for the treatment of:

• Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

• Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).¹

TAZVERIK is indicated for the treatment of:

Important Safety Information continued on back page of this insert. Please see Brief Summary of the Prescribing Information on the adjacent pages.
TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE
• TAZVERIK® (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
• TAZVERIK is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSE AND ADMINISTRATION
Patient Selection-Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens [see Clinical Studies]. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Swallow tablets whole. Do not cut, crush, or chew tablets. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Dose Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions, and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>600 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>400 mg orally twice daily</td>
</tr>
</tbody>
</table>

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia [see Adverse Reactions]</td>
<td>Neutrophil count less than 1 x 10^9/L</td>
<td>Withhold until neutrophil count is greater than or equal to 1 x 10^9/L or baseline. For first occurrence, resume at same dose. For second and third occurrence, resume at reduced dose. Permanently discontinue after fourth occurrence.</td>
</tr>
<tr>
<td>Thrombocytopenia [see Adverse Reactions]</td>
<td>Platelet count less than 50 x 10^9/L</td>
<td>Withhold until platelet count is greater than or equal to 75 x 10^9/L or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td>Anemia [see Adverse Reactions]</td>
<td>Hemoglobin less than 8 g/dL</td>
<td>Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.</td>
</tr>
<tr>
<td>Other adverse reactions [see Adverse Reactions]</td>
<td>Grade 3</td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first occurrence, resume at reduced dose. Permanently discontinue after second occurrence.</td>
<td></td>
</tr>
</tbody>
</table>

Dosage Modifications for Drug Interactions
Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

<table>
<thead>
<tr>
<th>Current Dosage</th>
<th>Adjusted Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg orally twice daily</td>
<td>400 mg orally twice daily</td>
</tr>
<tr>
<td>600 mg orally twice daily</td>
<td>400 mg for first dose and 200 mg for second dose</td>
</tr>
<tr>
<td>400 mg orally twice daily</td>
<td>200 mg orally twice daily</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS
Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC0-∞]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions].

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 safety of TAZVERIK was evaluated in two cohorts (Cohorts 4 and 5) of Study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 87 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The median number of prior therapies was 3 (range 1 to 11). Patients were required have a creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 36% of patients who received TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in ≥2% of patients was second primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in ≥3% of patients were thrombocytopenia and fatigue. Dose reduction due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions (≥20%) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAZVERIK N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>36</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>30</td>
</tr>
<tr>
<td>Lower respiratory tract infection*</td>
<td>17</td>
</tr>
<tr>
<td>Urinary tract infection*</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>22</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
</tr>
<tr>
<td>Rash*</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory and mediastinal system</td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>17</td>
</tr>
<tr>
<td>Nervous system</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 6 continues on the next page.
● Includes fatigue and anemia
● Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection
● Includes bronchitis, lower respiratory tract infection, tracheobronchitis
● Includes cystitis, urinary tract infection, urinary tract infection staphylococcal
● Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
● Includes back pain, limb discomfort, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, spinal pain
● Includes erythema, rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation
● Includes cough and productive cough
● Includes headache, migraine, sinus headache

Clinically relevant adverse reactions occurring in <10% of patients who received TAZVERIK included:
• Infection: sepsis (2%), pneumonia (2%), and herpes zoster (2%)

Table 7 summarizes select laboratory abnormalities in patients with follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 7. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</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>57</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>53</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

**DRUG INTERACTIONS**

**Effect of Other Drugs on TAZVERIK** - Strong and Moderate CYP3A Inhibitors:
Co-administration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations [see Clinical Pharmacology], which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose [see Dosage and Administration] Strong and Moderate CYP3A Inducers:
Co-administration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations [see Clinical Pharmacology], which may decrease the efficacy of TAZVERIK. Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK.

**Effect of TAZVERIK on Other Drugs** - CYP3A Substrates: Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates [see Use in Specific Populations, Clinical Pharmacology].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy** - Risk Summary: Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology], TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [AUC0-24h] at the 800 mg twice daily dose (see Data). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data - Animal Data: In pregnant rats, once oral daily administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily dose). Skeletal malformations and variations occurred in fetuses at doses of ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose), 250 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

**Lactation** - Risk Summary: There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

**Females and Males of Reproductive Potential** - Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK [see Use in Specific Populations]. Risk Summary: TAZVERIK can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Contraception: Females - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective [see Drug Interactions]. Males - Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

**Pediatric Use** - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

**Juvenile Animal Toxicity Data** - In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:
- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Dilated testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

**Geriatric Use** - Clinical studies of TAZVERIK did not include sufficient numbers of patients with relapsed or refractory follicular lymphoma aged 65 and over to determine whether they respond differently from younger subjects.

**Renal Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease [see Clinical Pharmacology].

**Hepatic Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN). TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment [see Clinical Pharmacology].

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML, have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. Tazemetostat did not cause genotoxic damage in a standard battery of studies including micronucleus, comet assay, and in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Gnomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs [see Use in Specific Populations].

**PATIENT COUNSELING INFORMATION** - Advise the patient to read the FDA-approved patient labeling (Medication Guide). Secondary Malignancies - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see Warnings and Precautions]. Embryo-Fetal Toxicity - Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations]. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations, Nonclinical Toxicology].

Lactation - Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose [see Use in Special Populations].

**Drug Interactions** - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit, and grapefruit juice while taking TAZVERIK [see Drug Interactions].

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Important Safety Information (continued)

- Embryo-Fetal Toxicity (continued)
  Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC 0-45h]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions
In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions
Avoid coadministration of strong and moderate CYP3A inhibitors with TAZVERIK, which may decrease the efficacy of TAZVERIK.

Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation
Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Before prescribing TAZVERIK, please read the Brief Summary of the Prescribing Information on the adjacent pages.

EZH2=enhancer of zeste homologue 2; MT=mutant type; WT=wild type.

References:
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Learn more about the approval of TAZVERIK for R/R FL patients based on efficacy demonstrated in both MT and WT EZH2 populations studied.¹

Visit ExploreTAZVERIK.com today
Emerging Therapies Expand Options in Lung Cancer

by MEIR RINDE

DURING THE PAST 12 months, the treatment landscape for patients with non-small cell lung cancer (NSCLC) has expanded dramatically with FDA approvals of the first drugs directed at KRAS G12C and EGFR exon 20 mutations as well as continued progress in developing new therapies for subsets of patients with other molecularly targetable alterations and with PD-L1-high disease (TABLE).1

New findings that shed light on the optimal use of liquid biopsies also are among the exciting advancements for patients with lung cancer, according to Benjamin P. Levy, MD. Levy, whose research has contributed to new therapeutic strategies for patients with thoracic malignancies, is clinical director of medical oncology at Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital in Washington, DC. He is also an associate professor of oncology at Johns Hopkins University School of Medicine in Baltimore, Maryland.

In November, Levy will help elucidate the latest data in the lung cancer field during the 39th Annual CFS®: Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow®, which he cochairs for the sixth consecutive year. Physicians’ Education Resource®, LLC (PER®) is hosting the 3-day event (November 3-5) as a hybrid meeting featuring live, interactive presentations in New York, New York, along with a virtual option.

At CFS®, leading experts will discuss practice-changing innovations in diagnosis, treatment, and supportive care that occurred over the past year across the spectrum of cancer types. The first day of the conference is devoted to hematologic malignancies, including acute leukemias, multiple myeloma, and myeloproliferative neoplasms. The second day includes sections on gynecologic and dermatoologic malignancies as well as pan-tumor topics. The third day features tracts on lung; head, neck, and thyroid cancers; gastrointestinal; and genitourinary cancers.

As he prepares for the conference, Levy marvels at how rapidly therapies for patients with lung cancer have advanced since he first helped lead the annual meeting. “What I’ve seen is pretty remarkable in terms of the changes in the topics that have happened over the past 5 years,” Levy said in an interview with OncologyLive®, “When I started, most of the talks were devoted to either chemotherapy or immunotherapy. The subject matter now has rapidly expanded to encompass all the new targeted therapies or immunotherapy combinations that are either under clinical investigation or FDA approved.”

Notably, topics will include a discussion of leveraging liquid biopsy into the diagnostic algorithm for lung cancer, an abiding subject of interest and research for Levy. With the utility of liquid biopsies now established for accurate genotyping of patients with lung cancer, new ways of using circulating tumor DNA (ctDNA) technology are being developed, he said.

“One is longitudinal assessment, looking at changes in ctDNA when patients are on a targeted therapy or immunotherapy as an early indicator of response or lack of response. The other strategy is looking in the minimal residual disease setting in patients who are cured and are being surveilled by scan. The question is, can you use ctDNA to detect recurrences earlier than a CT scan that then can inform treatment decisions? That’s really very, very exciting moving forward,” he said.
A FOCUS ON PRECISION APPROACHES

Of his many contributions to lung cancer research and oncology education, Levy is perhaps best known for his passion for biomarker testing and liquid biopsy in particular, as demonstrated by his enthusiasm for expanding the benefits of the assays for patients, colleagues say.

“He’s been an advocate for using ctDNA and blood-based platforms for quite some time. He was one of the early adopters of this technology and has contributed significantly through holding educational meetings and participating in studies. It ended up being an important component of what we do now. He gets a lot of credit for that,” said Hossein Borghaei, DO, MS, chief of the Division of Thoracic Medical Oncology and the Gloria and Edmund M. Dunn Chair in Thoracic Oncology at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Another focus of Levy’s work is the development and refinement of immunotherapy combinations for patients with EGFR-mutated NSCLC. He is serving as the Hopkins principal investigator on the phase 2 SAVANNAH trial (NCT03778229) evaluating the combination of savolitinib plus osimertinib (Tagrisso) in patients with EGFR-positive and MET-amplified locally advanced or metastatic NSCLC following progression on osimertinib. Savolitinib is an investigational MET tyrosine kinase inhibitor (TKI), and osimertinib is a third-generation EGFR TKI. Levy’s research also includes studies of targeted drugs both for lung cancer and other malignancies such as thyroid cancer.

“He was instrumental in the development of some of our most active targeted agents, including the recent selective RET inhibitors. In general, he’s done a lot to develop the field of targeted therapy, and it goes everywhere from testing to treatment. I’m grateful we have him on our front lines getting our message across,” said Stephen V. Liu, MD, director of thoracic oncology and developmental therapeutics at the Lombardi Comprehensive Cancer Center of Georgetown University in Washington, DC.

Levy also has been very active in education and professional development through the American Society of Clinical Oncology (ASCO). He participated in the organization’s year-long Leadership Development Program, was on the editorial board of the Journal of Clinical Oncology for 3 years, and served on committees involved in planning ASCO conferences and overseeing an online learning platform. He recently became editor in chief of the ASCO Self-Evaluation Program, which publishes a concise review of oncology topics for physician education.

“He’s always there to help you think through a tough case. He helps break down complex ideas and focuses on teachable moments,” Liu said. “He brings clarity to a lot of challenging clinical situations. He’s incredibly effective in that role, and that’s part of what makes Ben a great oncologist.”

NEW AND EMERGING THERAPIES

Levy’s CFS® cochairs are Ajai Chari, MD, Charu Aggarwal, MD, MPH, and the following approvals have been announced:

**TABLE. A Year of FDA Approvals in Lung Cancer**

<table>
<thead>
<tr>
<th>Date</th>
<th>Approval Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAY 2021</td>
<td>Sotorasib (Lumakras), a RAS GTPase family inhibitor, for adults with KRAS G12C-mutated locally advanced or metastatic NSCLC after at least 1 prior systemic therapy*</td>
</tr>
<tr>
<td>MAR 2021</td>
<td>Lorlatinib (Lorbrena) for patients with metastatic NSCLC with ALK-positive tumors, as detected by an FDA-approved testb</td>
</tr>
<tr>
<td>FEB 2021</td>
<td>Ceritinib-rwlc (Libtayo) for the first-line treatment of patients with advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation or who have metastatic disease) with a PD-L1 tumor proportion score of 50% or higher and no with EGFR, ALK, or ROS1 aberrationsa</td>
</tr>
<tr>
<td>DEC 2020</td>
<td>Osimertinib (Tagrisso) as adjuvant therapy after tumor resection in patients with NSCLC with tumors that have EGFR exon 19 deletions or exon 21 L858R mutationsa</td>
</tr>
<tr>
<td>SEP 2020</td>
<td>Pralsetinib (Gavreto) for adults with metastatic RET fusion-positive NSCLCa</td>
</tr>
<tr>
<td>JUN 2020</td>
<td>Lurbinectedin (Zepzelca) for adults with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapya</td>
</tr>
</tbody>
</table>

*Accelerated approval.  
bRegular approval.
targets for aberrations including KRAS G12C and HER2 and the targeting of gene fusions in adenocarcinomas, namely involving ALK, ROS1, RET, and NTRK.

Experts will also review competing frontline immunotherapy strategies for patients with lung adenocarcinoma; evolving treatment strategies for EGFR-mutated lung cancer, including those with exon 20 aberrations; precision medicine uses in early-stage lung cancer; management of squamous cell lung cancer; novel therapeutic strategies for small cell lung cancer (SCLC); and updates in mesothelioma.

Sotorasib

Levy said participants will discuss new agents aimed at mutations that were previously considered undruggable or very difficult to target. One of them is sotorasib (Lumakras), the first treatment for adults with NSCLC whose tumors harbor KRAS G12C mutations. In May, the FDA granted an accelerated approval for sotorasib for patients with the mutation who have received at least 1 prior systemic therapy. The agency also approved the QIAGEN therascreen KRAS RGQ PCR kit tissue test and the Guardant360 CDx plasma assay as companion diagnostics for sotorasib, with the recommendation that tumor tissue be tested if no mutation is detected in a plasma specimen.3

The decision was based on findings from the CodeBreaK 100 trial (NCT03600883), which involved patients with locally advanced or metastatic NSCLC with KRAS G12C mutations.5 Efficacy was evaluated in 124 patients with disease that progressed on or after at least 1 prior systemic therapy. Patients received sotorasib 960 mg orally daily until disease progression or unacceptable toxicity.

The median age among all participants (N = 126) was 63.5 years (range, 37-80) and 117 patients (92.9%) were former or current smokers. In all, 72 (57.1%) had received 2 or 3 prior lines of chemotherapy during the phase 1 multicohort CHRYSALIS trial (NCT02609776). The median age of participants was 62 years (range, 42-84), the median prior lines of therapy was 2 (range, 1-7), and 53% were never smokers.

The ORR was 40% (95% CI, 26%-54%), including a CR rate of 3.7% and a PR rate of 34%. The median DOR was 11.1 months (95% CI, 6.9-NE) and 63% of patients had a response lasting 6 months or longer.5

Among responders, the median duration of response (DOR) was 11.1 months (95% CI, 6.9-not estimable [NE]) and the median time to response was 1.4 months (range, 1.2-10.1). At the time of data cutoff on March 15, 16 (34.7%) patients who experienced a response were continuing therapy without disease progression. The median progression-free survival (PFS) among evaluable patients was 6.8 months (95% CI, 5.1-8.2).

Treatment-related adverse events (TRAEs) of any grade occurred in 88 (69.8%) patients in the overall population and led to discontinuation in 9 (7.1%) patients. Grade 3 TRAEs were reported in 25 (19.8%) patients, and 1 (0.8%) patient had grade 4 TRAEs (dyspnea/pneumonitis). Grade 3 events included alanine aminotransferase increase (6.3%), aspartate aminotransferase increase (5.6%), and diarrhea (4.0%). No fatal TRAEs were reported.4

Amivantamab

In May, the FDA also granted an accelerated approval for amivantamab-vmjw (Rybrevant), a bispecific antibody directed against EGFR and MET receptors, Levy noted. It was approved for adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, with disease that has progressed on or after platinum-based chemotherapy.5 The agent is the first targeted therapy approved after platinum-based chemotherapy during the phase 1 multicohort CHRYSALIS trial (NCT02609776). The median age of participants was 62 years (range, 42-84), the median prior lines of therapy was 2 (range, 1-7), and 53% were never smokers.

The ORR was 40% (95% CI, 26%-54%), including a CR rate of 3.7% and a PR rate of 34%. The median DOR was 11.1 months (95% CI, 6.9-NE) and 63% of patients had a response lasting 6 months or longer.5

All-grade adverse events (AEs) occurring in 10% or more of patients in the safety population (N = 129) included rash (84%), infusion-related reactions (IRRs; 64%), and paronychia (50%).
In 10-15 minute increments over the course of a few days, I can be caught up with the most relevant up-to-the-minute standards in clinical oncology.

– 2020 Attendee
Grade 3 or 4 AEs included rash (3.9%) and IRRs, paronychia, and diarrhea, each at 3.1%.

**Trastuzumab deruxtecan**

CF5 presenters also will discuss promising data for fam-trastuzumab deruxtecan-nxki (Enhertu), an antibody-drug conjugate (ADC) approved in HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma settings. In lung cancer, trastuzumab deruxtecan is being studied in the phase 2 DESTINY-Lung02 trial (NCT04644237) in patients with HER2-mutated metastatic NSCLC with disease recurrence or progression during or after at least 1 prior platinum-containing treatment regimen. The drug has a breakthrough therapy designation and could be approved later this year, Levy said.

Trastuzumab deruxtecan showed promising efficacy in interim findings from the phase 2 DESTINY-Lung01 study (NCT03505710) in patients with nonsquamous NSCLC that overexpresses HER2 or harbors a HER2 activating mutation. At a median treatment duration of 7.76 months (range, 0.7-14.3), the confirmed ORR by independent central review among 42 patients was 61.9% (95% CI, 45.6%-76.4%). At data cutoff, median DOR was not reached and 16 of 26 responders remained on treatment. The estimated median PFS was 14.0 months (95% CI, 6.4-NE). The median treatment duration of 7.76 months (range, 0.7-14.3), the confirmed ORR by independent central review among 42 patients was 61.9% (95% CI, 45.6%-76.4%). At data cutoff, median DOR was not reached and 16 of 26 responders remained on treatment. The estimated median PFS was 14.0 months (95% CI, 6.4-14.0).

All patients had treatment-emergent adverse events (TEAEs); 64.3% were grade 3 or worse, including 52.4% that were deemed related to the drug. TEAEs included decreased neutrophil count (26.2%) and anemia (16.7%). There were 5 cases (11.9%) of grade 2 drug-related paronychia, and diarrhea, each at 3.1%. Included were 5 cases (11.9%) of grade 2 drug-related paronychia, and diarrhea, each at 3.1%. There were 5 cases (11.9%) of grade 2 drug-related paronychia, and diarrhea, each at 3.1%.

The data for these drugs are encouraging, Levy said. “Those are 3 exciting drugs that we have—2 now approved, 1 potentially approved—and the list keeps getting longer and longer,” he said.

**More novel therapies for NSCLC**

Although no ADCs are currently approved for lung cancer indications, clinical studies are advancing for several candidates besides trastuzumab deruxtecan, suggesting the potential for a new class of therapies. “These are, I think, really good efforts [for drugs] that we’re just beginning to learn about,” Levy said.

Levy is among the leading investigators evaluating datopotamab deruxtecan (DS-1062a) in patients with NSCLC as part of the phase 1 TROPION-PanTumor01 trial (NCT04310385). The novel ADC incorporates an antibody directed at TROP2. Also advancing is patritumab deruxtecan (U3-1402), a ADC directed at HER3 that is being tested in patients with metastatic or locally advanced EGFR-mutated NSCLC in the phase 2 HERTHEMA-Lung01 study (NCT04619004).

Meanwhile, Levy also is pursuing studies of repotrectinib (TPX-0005), a next-generation TKI of ROS1 and TRK. He is serving as the Hopkins principal investigator on the phase 1/2 TRIDENT-1 study (NCT03093116) evaluating repotrectinib in patients with advanced NSCLC with ROS1 or NTRK1/2/3 gene rearrangements.

**Activity in SCLC**

At CFS6, Liu is scheduled to discuss novel therapeutic strategies for SCLC. Since 2019, the FDA has approved combining chemotherapy with the PD-L1 inhibitors atezolizumab (Tecentriq) or durvalumab (Imfinzi) for the first-line treatment of patients with extensive-stage SCLC. Additionally, Levy noted the accelerated approval in June 2020 of lurbinectedin (Zepzelca), a chemotherapy agent, for treating adults with metastatic SCLC that has progressed after chemotherapy.9

Promising therapies in development include tarlatamab (AMG 757), a bispecific T-cell engager targeting DLL3 that is being tested as monotherapy and in combination with pembrolizumab (Keytruda) in a phase 1 trial (NCT03319940).

**UNDERSTANDING THE ROLE OF IMMUNOTHERAPY**

**Earlier settings**

Levy highlighted several other key areas of research that will be discussed during the CFS7 lung session, including efforts to take advantage of immunotherapy earlier in the treatment process.

“What has happened over the past, essentially 6 months, is that we’re starting to understand how to leverage immunotherapy for cure. We’re looking at immunotherapy potentially in the neoadjuvant space, prior to surgical resection, and then based on the most recent data that were presented at ASCO, looking at it in the adjuvant setting,” he said.

Findings from the phase 3 IMpower010 trial (NCT02486718) show that adjuvant treatment with atezolizumab led to a significant improvement in disease-free survival (DFS) vs best supportive care (BSC) in patients with resected stage II to IIIA NSCLC, particularly those with PD-L1-positive tumors.10

In patients with at least 1% PD-L1 expression, the median DFS was NE (95% CI, 36.1-NE) with atezolizumab (n = 248) vs 35.5 months (95% CI, 29.0-NE) for those who received BSC (n = 228), which translated into an HR of 0.66 (95% CI, 0.50-0.88; P = .004). The 2-year DFS rate was 74.6% with atezolizumab vs 61.0% with BSC. The 3-year DFS rates were 60.0% and 48.2%, respectively.

The benefit was less pronounced in all randomized patients with stage II to IIIA disease. The median DFS was 42.3 months (95% CI, 36-NE) among patients treated with atezolizumab (n = 442) vs 35.3 months (95% CI, 30.4-46.4) for those who received BSC (n = 440), which translated to an HR of 0.79 (95% CI, 0.64-0.96; P = .02). The 2-year DFS rate was 70.2% with atezolizumab vs 61.6%...
with BSC and the 3-year rates were 55.7% and 49.4%, respectively.

“I would be comfortable considering using that therapy,” Levy observed. “This is an unmet need. These patients have historically aggressive diseases and we need to do better.”

**Liquid biopsy biomarkers**

Levy noted that liquid biopsy is being studied as a way to measure response to immunotherapy. At CFS®, Charu Aggarwal, MD, MPH, will discuss her recent study that used serial monitoring of ctDNA by next-generation gene sequencing as a biomarker of response and survival in patients with advanced NSCLC receiving pembrolizumab-based therapy.11 Aggarwal is the Leslye M. Heisler Associate Professor for Lung Cancer Excellence at Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Aggarwal and colleagues found that molecular response values based on changes in ctDNA were significantly lower in patients with an objective radiologic response compared with nonresponders (log mean 1.25% vs 27.7%; P < .001). Patients achieving a durable clinical benefit had significantly lower molecular response values compared with patients with no durable benefit (log mean 3.5% vs 49.4%; P < .001). Molecular responders also had significantly longer PFS (HR, 0.25; 95% CI, 0.13-0.50) and overall survival (HR, 0.27; 95% CI, 0.12-0.64) compared with molecular nonresponders.

The results suggest that a reduction in ctDNA levels during treatment correlates with better outcomes and that assessments during therapy may yield a noninvasive method of predicting long-term efficacy of pembrolizumab therapy, investigators concluded.

“The big, broad question is: Are ctDNA changes more accurate or a more accurate surrogate for what a patient’s cancer is doing, vs a CT scan, which is a pretty rudimentary platform where you’re looking at a 2-dimensional thing,” Levy said. “It’s tough to know what’s going on, and maybe 50 DNA changes are a better indicator…We should be able to find out how to act on these changes.”

Levy is hoping to help advance the utility of liquid biopsies through a large phase 2 trial (NCT04410796) in which patients with metastatic EGFR-mutant NSCLC will receive first-line osimertinib therapy. Participants with persistent ctDNA detected in plasma samples will then be randomized to receive either osimertinib alone or with chemotherapy. MSK investigators are leading the study, which aims to recruit 571 patients throughout the United States.

**Impact on mutations**

Levy has made a number of contributions to the development of immunotherapies. He led or participated in several studies of checkpoint inhibitors, such as nivolumab (Opdivo) in refractory squamous NSCLC and durvalumab as third-line or later treatment for advanced NSCLC.12,13

One outstanding question is how to use immunotherapy when treating patients with NSCLC with driver mutations, Levy said. “This field is sort of dichotomized into those patients who get targeted therapies and those who get immunotherapies. We’re still trying to understand how to leverage immunotherapy in the targeted therapy space,” he said.

Numerous studies are seeking to clarify immunotherapy’s role. Levy is on the steering committee for the phase 2 TH-138 study (NCT03786692) evaluating the addition of an immunotherapeutic agent to the combination of antiangiogenic therapy plus a platinum doublet. Investigators seek to recruit 117 patients who have stage IV nonsquamous NSCLC with tumors harboring an EGFR exon 19 or 21 mutation or who are never smokers with wild-type tumors.14 Patients with an EGFR mutation must have progression after receiving prior TKI therapy, and those with wild-type tumors must be treatment naïve. Participants will be randomized to receive carboplatin, pemetrexed (Alimta), and bevacizumab (Avastin) with or without atezolizumab.

The rationale for the study stems from prior trial findings suggesting such combinations may overcome resistance to PD-L1 inhibitors in these patients. Fox Chase Cancer Center and the National Comprehensive Cancer Network are sponsoring the study.14

“There are tremendous efforts going on across the country, looking at sorting out mechanisms of resistance and then determining what to do when you discover a mechanism of resistance,” Levy said.

For Levy, the pursuit of individualized therapies for patients with lung cancer is a mission that began during a hematology/oncology fellowship at New York Weill Cornell Hospital in the mid-2000s. He started with a focus on prostate cancer research but shifted to lung cancer because at that time there were few options for patients.

“I had a real connection to potentially personalized medicine that was starting to take shape in lung cancer,” Levy said. “We had this single [target] with EGFR mutations potentially being druggable. Who would have thought in just a short time that there would be 10 more genes in non–small cell cancer that would be wedded to a targeted therapy?”

**IMPORTANCE OF ADDRESSING RESISTANCE**

As investigators continue to explore new therapies, the development of strategies for overcoming resistance has emerged as one of the most pressing needs in the field today, Levy said.

“We have multiple immunotherapeutic options to offer patients without a targetable mutation, with many of these eliciting meaningful and durable responses. The question is, what do you do when there’s disease progression? What are the mechanisms of resistance and how do we act on those moving forward?” he said.

He noted that similar questions to those being asked about immunotherapy apply to targeted therapies as well. Despite the substantial new benefits they have provided to patients with matching genotypes over the past several years, oncologists who treat patients with NSCLC still have much to learn about the best ways to use the agents and what to do when they stop working, Levy said.

“What do you do when resistance develops, what are those mechanisms of resistance, and how should we act on them? That’s a big question for targeted therapy. Are there optimal combination strategies with these newer targeted therapies such as bispecific antibodies or antibody drug conjugates? Should leverage these newer novel agents as stand-alone therapies? Or should we be adding other combination therapies like chemotherapy? That is clearly a real unmet need for patients with the right genotype,” he said.
"We have some unfinished business!"

INDICATION
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION
HEMMORHAGE
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Please see Important Safety Information and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
Adding CYRAMZA to paclitaxel nearly doubles the response vs paclitaxel alone\(^1,2\)

**ORR (Complete and Partial Response): Supportive Outcome Measure**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel (n=330)</th>
<th>Placebo + paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>28%</strong> (\text{median} 23, 33)</td>
<td><strong>16%</strong> (\text{median} 13, 20)</td>
</tr>
</tbody>
</table>

P<0.001

**Overall Survival: Major Outcome Measure Median-Months (95% CI)**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel (n=330)</th>
<th>Placebo + paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9.6</strong> (\text{median} 8.5, 10.8)</td>
<td><strong>7.4</strong> (\text{median} 6.3, 8.4)</td>
</tr>
</tbody>
</table>

Hazard ratio=0.81 \(0.68, 0.96\); \(P=0.017\)

**PFS: Supportive Outcome Measure Median-Months (95% CI)**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel (n=330)</th>
<th>Placebo + paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.4</strong> (\text{median} 4.2, 5.3)</td>
<td><strong>2.9</strong> (\text{median} 2.8, 3.0)</td>
</tr>
</tbody>
</table>

Hazard ratio=0.64 \(0.54, 0.75\); \(P<0.001\)

**STUDY DESIGN:** The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m² on days 1, 8, and 15 of each 28-day cycle.

**SELECT IMPORTANT SAFETY INFORMATION**

**GASTROINTESTINAL PERFORATIONS**
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from \(<1\%\).
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**IMPAIRED WOUND HEALING**
- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Please see Important Safety Information on next page and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
**IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)**

**Warnings and Precautions**

**Hemorrhage**
- CYRAMZA increased the risk of hemorrage and gastrointestinal hemorrhage, including Grade ≥ 3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

**Gastrointestinal Perforations**
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**Impaired Wound Healing**
- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

**Arterial Thromboembolic Events (ATEs)**
- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

**Hypertension**
- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. In 1116 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-24%. Grade 3-5 hypertension incidence ranged from 6-19%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions (IRR)**
- IRR, including severe and life threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR included rigor/hypotension, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

**Worsening of Pre-existing Hepatic Impairment**
- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (6%).

**Posterior Reversible Encephalopathy Syndrome (PRES)**
- PRES (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

**Proteinuria Including Nephrotic Syndrome**
- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥ 3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

**Thyroid Dysfunction**
- In 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

**Embryo-Fetal Toxicity**
- CYRAMZA can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

**Lactation**
- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

**Adverse Reactions**

**REGARD:**
- The most common adverse reactions (All Grades) observed in single agent CYRAMZA-treated gastric cancer patients at a rate of ≥5% and ≥2% higher than placebo were hypertension (16% vs 8%), diarrhea (14% vs 9%), headache (9% vs 3%), and hypertension (6% vs 2%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were: neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥ 3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

**RAINBOW:**
- The most common adverse reactions (All Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue (36% vs 29%), anemia (28% vs 19%), neutropenia (28% vs 16%), diarrhea (24% vs 13%), hypertension (18% vs 8%), peripheral edema (14% vs 7%), proteinuria (14% vs 6%), thrombocytopenia (13% vs 6%), and dyspepsia (12% vs 6%).
- The most common serious adverse reactions with CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%). 11% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and ≤5% of patients receiving CYRAMZA with paclitaxel were sepsis (1.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

Please see Brief Summary of Prescribing Information for CYRAMZA on next page.

**References:**
Gastric Cancer

CYRAMZA, as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy.

CONTRAINdications

None.

WARNINGS AND PRECAUTIONS

Hemorrhage

CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrolment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Gastrointestinal Perforations

CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway, CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds. Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety and resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%. Permanently discontinue CYRAMZA in patients who experience an ATE.

Hypertension

An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies, excluding REGARD, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure two to more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-related Reactions

Infusion-related reactions (IRR), including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. The most common serious adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients were hypertension and diarrhea. Table 1 provides the frequency and severity of adverse reactions observed in patients receiving CYRAMZA with paclitaxel at a rate of ≥30% and ≥3% higher than placebo.

Table 1: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in REGARD

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CYRAMZA (N=236)</th>
<th>Placebo (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Nervous System</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

* Hypertension is a consolidated term.

Clinically relevant adverse reactions reported in >1% and <5% of CYRAMZA-treated patients in REGARD were hypotension (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%). Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.6% and the rate of IRR was 0.4%.

CYRAMZA Administered in Combination with Paclitaxel (RAINBOW)

Patients received paclitaxel 80 mg/m² on Days 1, 8, and 15 of each 28-day cycle with either CYRAMZA 8 mg/kg or placebo intravenously every two weeks. Patients randomized to CYRAMZA received a median of 9 doses; the median duration of exposure was 18 weeks, and 93 (28% of 327) patients received CYRAMZA for at least six months.

The most common serious adverse reactions in patients who received CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%). 10% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors. Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%). The most common adverse reactions (all grades) observed in patients who received CYRAMZA with paclitaxel at a rate of ≥30% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia, neutropenia, diarrhea, and epistaxis. Table 2 provides the frequency and severity of adverse reactions observed in patients receiving CYRAMZA with paclitaxel at a rate of ≥30% and ≥3% higher than placebo.

Table 2: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in RAINBOW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CYRAMZA + Paclitaxel (N=237)</th>
<th>Placebo + Paclitaxel (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Fatigue/Asthema</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Hematology</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage events</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

* Neutropenia, gastrointestinal hemorrhage events, hypertension, proteinuria, and hypoalbuminemia are consolidated terms.

† Includes 1 fatal event in the CYRAMZA arm.

Clinically relevant adverse reactions reported in >1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.
Immunogenicity

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

In clinical trials, 86/2890 (3%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CYRAMZA. Because such reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Blood and lymphatic system: Thrombotic microangiopathy
- Neoplasms benign, malignant and unspecified: Hemangioma
- Respiratory, thoracic, and mediastinal: Dysphonia
- Vascular-Arterial (including aortic) aneurysms, dissections, and rupture

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman. There are no available data on CYRAMZA use in pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise a pregnant woman 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 2-4% and 15-20%, respectively.

Data

Animal Data

No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryo-fetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and fetoplacental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forlimb, forebrain, heart, and blood vessels.

Lactation

Risk Summary

There is no information on the presence of ramucirumab in human milk or its effects on the breastfed child or on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating.

Contraception

Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

Infertility

Females

Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use

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

Juvenile Animal Toxicity Data

In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use

Of the 563 CYRAMZA-treated patients in REGARD and RAINBOW, 205 (36%) were 65 and over, while 41 (7%) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger subjects.

Of the 221 patients who received CYZAMZA with erlotinib in RELAY, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Overall, no clinically meaningful differences in effectiveness were observed between these patients and younger patients. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (52% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 8%).

Of the 1253 patients in REVEL, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA with docetaxel in REVEL, 237 (38%) were 65 and over, while 46 (7%) were 75 and over. In an exploratory subgroup analysis of REVEL, the hazard ratios for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years and over was 1.10 (95% CI: 0.89, 1.36).

Of the 525 patients who received CYRAMZA with FOLFIRI in RAISE, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

No dose adjustment is recommended for patients with mild (total bilirubin within ULN and aspartate aminotransferase (AST) >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA.

Additional information can be found at www.cyramza.com
Experts Take Stock of Pivotal Trials at ASCO 2021

by GINA MAURO

THE 2021 AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) Annual Meeting’s virtual format continued for a second year. The agenda encompassed more than 2450 abstracts across a variety of malignancies, a plethora of which had results that experts say have practice-changing potential.

OncologyLive® heard from leading oncologists in breast cancer, gastrointestinal cancers, genitourinary cancers, gynecologic malignancies, multiple myeloma, and lung cancer, who shared their perspectives on the biggest abstracts being presented at ASCO 2021.

BREAST CANCER
Harold J. Burstein, MD, PhD
Dana-Farber Cancer Institute
Boston, MA

OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer (Abstract LBA1)

In the double-blind, multicenter, phase 3 OlympiA trial (NCT02032823), investigators explored the safety and efficacy of olaparib (Lynparza) tablets vs placebo as an adjuvant treatment for patients with BRCA1-mutated, high-risk HER2-negative early breast cancer. Patients had to have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

The 36-month invasive disease-free survival (iDFS) rate for patients in the intention-to-treat population was 85.9% for those treated with olaparib (n = 921) vs 77.1% for those who received placebo (n = 915; HR, 0.58; 99% CI, 0.41-0.82; P < .0001). An 8.8% (95% CI, 4.5%-13.0%) 3-year iDFS rate difference was reported. Fewer deaths were reported with olaparib, but the overall survival (OS) benefit was not statistically significant (59 vs 86 deaths, respectively; HR, 0.68; 99% CI, 0.44-1.05; P = .024).

“OlympiA [is the] adjuvant olaparib trial for BRCA1/2-associated breast cancers. If clinically compelling, then [this] adds a new selective therapy and would lead to near universal genetic testing after breast cancer diagnosis.”

A randomized phase III post-operative trial of platinum-based chemotherapy (P) versus capecitabine (C) in patients (pts) with residual triple-negative breast cancer (TNBC) following neoadjuvant chemotherapy (NAC): ECOG-ACRIN EA1131 (Abstract 605)

Regardless of treatment with capecitabine or platinum-based chemotherapy, the reported 3-year iDFS rate from a phase 3 trial (NCT02445391) was lower than expected for patients with stage II/III triple-negative breast cancer (TNBC) with residual disease following neoadjuvant chemotherapy.
Specifically, at the data cutoff of April 7, 2021, 308 patients with basal subtype TNBC (78% total accrual) were available for evaluation. For the 148 patients who received capecitabine the 3-year iDFS rate was 49% (95% CI, 39%-59%) compared with 42% (95% CI, 30%-53%) for the 160 patients who received adjuvant platinum therapy (HR, 1.06; 95% reliable chain index, 0.62-1.81).

The findings suggest that for patients with TNBC and residual disease there is no role for adjuvant platinum agents after neoadjuvant taxanes/anthracycline chemotherapy regardless of intrinsic subtype. The trial was halted in March 2021.

“Adjuvant carboplatin was not better than capecitabine for residual cancer after neoadjuvant chemotherapy for TNBC. [This shows that] capecitabine is the treatment of choice, and it makes one question the carboplatin role overall.”

De-escalated neoadjuvant pertuzumab + trastuzumab with or without paclitaxel weekly in HR-/HER2+ early breast cancer: ADAPT-HR-/HER2+ biomarker and survival results (Abstract 503)

According to earlier reported results from the cohort of patients with hormone receptor-negative, HER2-positive breast cancer enrolled in the ADAPT trial (NCT01779206), 12 weeks of neoadjuvant paclitaxel, pertuzumab (Perjeta), and trastuzumab (Herceptin) led to a 90.5% pathologic complete response (pCR) rate (n = 42) compared with 34.4% for those treated with pertuzumab and trastuzumab alone (n = 92).

At 2021 ASCO, the West German Study Group investigators presented the 5-year iDFS rates from the trial, which were 87% (95% CI, 78%-96%) and 98% (95% CI, 84%-100%), respectively (HR, 0.32; 95% CI, 0.07-1.47; P = .144).

“The addition of liposomal irinotecan (nal-IRI) to 5-fluorouracil/leucovorin (5-FU/ LV) showed a significant improvement in progression-free survival (PFS) and overall survival (OS) in patients with biliary tract cancer after progression on gemcitabine and cisplatin, according to NIFTY trial (NCT03524508) results. Further, the treatment may well be considered standard in second-line therapy for this population. Patients in the trial received nal-IRI plus 5-FU/LV (n = 88) or 5-FU/LV alone (n = 86) every 2 weeks until disease progression or unacceptable toxicity. At a median follow-up of 11.8 months the median PFS with nal-IRI was 7.1 months (95% CI, 3.6-8.8) compared with 1.4 months with 5-FU/LV alone (HR, 0.56; 95% CI, 0.39-0.81; P = .0019). The median OS was 8.6 months (95% CI, 5.4-10.5) vs 5.5 months (95% CI, 4.7-7.2) in the experimental and control arms, respectively (HR, 0.68; 95% CI, 0.48-0.98; P = .0349). Further, the 6-month and 1-year OS rates for patients who received nal-IRI were 60.7% (95% CI, 50.3%-71.2%) and 35.4% (24.9%-45.9%). For those who received 5-FU/LV alone the OS rates were 45.9% (95% CI, 35.3%-56.5%) and 22.4% (95% CI, 13.1%-31.7%), respectively.

“NIFTY is a relatively large, randomized phase 2b study comparing nal-IRI and infusional 5-FU [i5-FU] vs i5-FU. The primary end point of this study was PFS, with OS, objective response rate (ORR) and safety as secondary end points. The study reached its primary end point, with more than doubling of the median PFS with nal-IRI/i5-FU vs i5-FU. There were significant improvements with [median] OS and ORR as well, with an expected toxicity profile. Prior data with FOLFOX from ABC06 [NCT01926236] did confirm an improvement starting chemotherapy. Updated findings showed that the PD-L1 inhibitor significantly improved long-term outcomes of these patients, eliciting a 3-year iDFS rate of 85.6% (n = 88) compared with 77.2% for those who received placebo (n = 86; HR, 0.48; 95% CI, 0.24-0.97; P = .0398). Further, the 3-year distant DFS and OS rates were significantly improved at 91.7% vs 78.4% (HR, 0.31; 95% CI, 0.13-0.74; P = .0078) and 95.2% vs 83.5% (HR, 0.24; 95% CI, 0.08-0.72; P = .0108), respectively.

“Neoadjuvant durvalumab improves pCR in TNBC, and now shows an OS benefit. [This] likely supports an approval for checkpoint inhibitors in stage II/III TNBC.”

Liposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic biliary tract cancer (BTC) after progression on gemcitabine plus cisplatin (GemCis): Multicenter comparative randomized phase 2b study (NIFTY) (Abstract 4006)
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in all outcomes [with modified FOLFOX] vs [active symptom control]. The relative concern from ABC06 included the fact that it was not compared to an active control (such as i-FU) and the overlapping risk of neurotoxicity with oxaliplatin following cisplatin. As such, I think the results of NIFTY are meaningful enough to consider the combination as an option for select patients, pending confirmation in a larger randomized controlled trial.”

This phase 3 study aimed to answer whether neoadjuvant multimodal treatment with carboplatin/paclitaxel plus radiation therapy (RT), known as CROSS, is more effective than perioperative chemotherapy regimens in patients with locally advanced esophageal cancer and esophageagastic junction adenocarcinoma. However, the design was changed to focus on a noninferior outcome vs a superiority one. Data showed that perioperative chemotherapy is not inferior to CROSS in this setting, with 3-year survival rates reported as 57% (n = 180) and 56% (n = 175), respectively (HR, 1.02; 95% CI, 0.74-1.42).

“The study was closed to accrual at the request of the Data Safety Monitoring Board, given the absence of futility. In other words, the 2 strategies appear to produce similar survival outcomes, putting into question the 2 strategies appear to produce similar survival outcomes, putting into question the need to be exposed to chemotherapy, its potential toxicities, and the lack of meaningful long-term efficacy. A previous argument made about a certain percentage of patients who may be ‘hyperprogressors’—a concept that has no scientific validity—is now disproved by the fact that OS is improved with nivolumab [as published] in a recent publication. The updated presentation continues to suggest meaningful benefits from nivolumab in this setting.”

Data from CheckMate 577 (NCT02743494) served as the basis for the May approval of adjuvant nivolumab (Opdivo) in patients with completely resected esophageal or gastro-esophageal junction cancer with residual pathologic disease who have received neoadjuvant chemotherapy. In this trial, the data showed a doubling in the median disease-free survival (DFS) vs placebo at 22.4 months and 11.0 months, respectively, leading to a 31% reduction in the risk of disease recurrence or death (HR, 0.69; 96.4% CI, 0.56-0.86; P = .0003).

At the 2021 ASCO Annual Meeting, additional efficacy data showed that PFS2 favored nivolumab vs placebo with an HR of 0.77 (95% CI, 0.60-0.99). Specifically, the time to second progression was not reached (95% CI, 34.0-not estimable) in the nivolumab arm vs 32.1 months (95% CI, 24.2-not estimable) in the placebo arm. Adjuvant nivolumab also demonstrated an acceptable safety profile, and quality of life was maintained for patients post treatment.

“CheckMate 577 compared the effects of nivolumab vs placebo in patients who received neoadjuvant CRT [chemoradiotherapy] with residual pathologic disease prior to inclusion. This study is transformational as it shows a doubling of the DFS with nivolumab vs placebo, [as published] in a recent publication. The updated presentation continues to suggest meaningful benefits from nivolumab in this setting.”

At the 2020 ASCO Virtual Scientific Program, data were presented from the pivotal the KEYNOTE-177 trial (NCT02563002) with pembrolizumab (Keytruda) in the frontline setting for patients with unresectable or metastatic microsatellite instability-high (dMMR) colorectal cancer (mCRC). The agent was approved in June 2020 for this patient population based on KEYNOTE-177 data.

The final OS data from KEYNOTE-177 presented at ASCO 2021 did not show a statistically significant reduction in mortality. The median OS was not reached (95% CI, 49.2-not reached) with pembrolizumab compared with 36.7 months (95% CI, 27.6-not reached) with chemotherapy (HR, 0.74; 95% CI, 0.53-1.03; P = .0359).

Although some results were not statistically significant, Bekaii-Saab said it still cements pembrolizumab as the frontline standard of care for this patient population.

“KEYNOTE-177 first reported out in 2020 when it met one of its coprimary end points, PFS, which was double that of the control arm. The median OS results are now being reported, showing again a positive outcome with an improvement for pembrolizumab vs chemotherapy/biologic of choice with an [HR] of 0.74, although not statistically significant. The high response rate and its durability continue to favor pembrolizumab.

The same is true for the toxicity profile and QOL [quality-of-life] measures. The updated results continue to confirm that the standard of care for first-line treatment for all patients with MSI-H mCRC should be pembrolizumab. At least 40% of patients with MSI-H mCRC experience durable remissions and will be spared the need to be exposed to chemotherapy, its potential toxicities, and the lack of meaningful long-term efficacy. A previous argument made about a certain percentage of patients who may be ‘hyperprogressors’—a concept that has no scientific validity—is now disproved by the fact that OS is improved with pembrolizumab [or at least not adversely affected by the first initiation of pembrolizumab including in non-responders]. These are great and very meaningful results for this small percentage of patients [5% of mCRC].”

Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577 (Abstract 4003)

Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (modified MAGIC or FLOT protocol) (NCT01726452) (Abstract 4004)

Final overall survival for the phase III KN177 study: Pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) (Abstract 3500)

At the 2020 ASCO Virtual Scientific Program, data were presented from the pivotal the KEYNOTE-177 trial (NCT02563002) with pembrolizumab (Keytruda) in the frontline setting for patients with unresectable or metastatic microsatellite instability-high (dMMR) colorectal cancer (CRC). The agent was approved in June 2020 for this patient population based on KEYNOTE-177 data.

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multi-center, open-label study (DESTINY-CRC01) (Abstract 3505)

Fam-trastuzumab deruxtecan-nxki (Enhertu) studied in patients with HER2-expressing, RAS wild-type metastatic CRC demonstrated continued efficacy in this setting in the
“Trastuzumab deruxtecan is an antibody-drug conjugate bound by a linker to a topoisomerase I inhibitor. T-DXd has shown interesting activity across a spectrum of HER2-overexpressing malignancies. Here, the authors presented updated long-term efficacy and safety data. ORR, the primary end point of this study, is 45% and did not appear to be affected by prior treatment with other anti-HER2 therapies. Not surprisingly, patients with IHC 2+/ or IHC 1+ did not exhibit any meaningful activity, while IHC 2+/ISH+ were associated with a very modest response rate.

“This study continues to illustrate the importance of testing for HER2 amplification early in the setting of mCRC. Although this remains a small subgroup of patients [2% to 4%], the implications of finding HER2 amplification in a RAS wild-type patient [include no probability of a response to EGFR inhibitors, but importantly, [do include] eligibility for treatment with HER2-targeted strategies. The results from DESTINY-CRC01 confirm the role of trastuzumab deruxtecan in HER2-amplified RAS wild-type mCRC. However, where [do we] place this therapy? Given the high risk of toxicities including the potential lethal risk of interstitial lung disease, trastuzumab deruxtecan’s preferred placement would be following failure of dual HER2-targeted therapy, such as following tucatinib [Tukysa] and trastuzumab [Herceptin] on the MOUNTAINEER study [NCT03043313]. Additional reasoning for placing trastuzumab deruxtecan in patients with prior exposure to anti-HER2 targeted therapies is supported by the maintained benefit in this setting, as shown in DESTINY-CRC01.”

In VISION (NCT03511664), an international, prospective, randomized, open-label, multicenter, phase 3 study, investigators assessed the efficacy and safety of 177lutetium (Lu)-prostate specific membrane antigen (PSMA)-617 plus investigator-chosen best standard of care compared with best standard of care alone (HR, 0.62; 95% CI, 0.52-0.74; 15.3 months vs 11.3 months with standard with 177Lu-PSMA-617 the median OS was presented data that showed the trial met both primary end points of OS and PFS, and the agent was granted a breakthrough therapy designation in June.

Specifically, in 551 patients treated with 177Lu-PSMA-617 the median OS was 15.3 months vs 11.3 months with standard of care alone (HR, 0.62; 95% CI, 0.52-0.74; P < .001). The median radiographic PFS analysis showed that the addition of 177Lu-PSMA-617 more than doubled time to progression at 8.7 months vs 3.4 months, respectively (HR, 0.40; 99.2% CI, 0.29-0.57; P < .001).

“This trial met both primary end points, which were a significant improvement in OS and radiographic PFS in patients with PSMA-positive mCRPC. In this trial, patients who had progressive PSMA-targeted mCRPC were randomized to treatment with 177Lu-PSMA-617 vs best standard of care alone.”

KEYNOTE-564 (NCT03142334) met its primary end point of disease-free survival (DFS) with pembrolizumab for the potential adjuvant treatment of patients with renal cell carcinoma (RCC) following nephrectomy or following nephrectomy and resection of metastatic lesions. At a median follow-up of 24.1 months the median DFS was not reached for patients who received pembrolizumab (n = 496) or those who received placebo (n = 498; HR, 0.68; 95% CI, 0.53-0.87; P = .0010). The 12-month and 24-month DFS rates were 85.7% and 77.3% in the pembrolizumab arm compared with 76.2% and 68.1% in the placebo arm.

“The ASCO plenary session included the results from the phase 3 KEYNOTE-564 study, which evaluated pembrolizumab, a PD-1 inhibitor, in the adjuvant setting of patients with RCC following nephrectomy and resection of metastatic lesions. As we know, these patients, when they have had successful surgical resection of RCC and some of the metastatic disease sites, have been rendered [as having] what we call [no evidence of}
Finally, in their analysis of the real-world community oncology setting, investigators explored the impact of new evidence on treatment selection for patients with mCSPC. They noted that over half of patients did not receive first-line treatment intensification over the study period, despite it being known to improve outcomes over androgen deprivation therapy alone.

“In the past 5 years, we have seen multiple phase 3 trials with mCSPC where the drugs were [initially] used or approved for mCRPC. When these drugs got moved to the up-front setting, they showed a dramatic improvement in OS. These drugs are docetaxel, abiraterone acetate [Zyarga], enzalutamide [Xtandi], and apalutamide [Erleada]. All 4 are now approved in the mCSPC setting, and the first one to be endorsed by all the guidelines was docetaxel in 2015. In the span of 2, 3, 4 years, all [these] oral pills got approval.

These improvements in OS with these drugs are not trivial. [We are not talking of] months, but of 1 to 2 years. I would assume that when we see this magnitude of OS benefit, our patients in the real world are being treated with these medications. The practice-changing trials were presented at ASCO and published in the New England Journal of Medicine. You would assume that these trials are going to change, and in fact have changed, the practice in the real-world population.

[In abstracts 5072 and 5073] there was an acceptably low utilization of these life-prolonging agents in patients with mCSPC in the United States. We like to believe that we spend so much money per capita per patient. We have one of the biggest, most well-resourced health system on the planet. In this health system and in this patient population, what we saw was really astounding. If you look at abstract 5073, you’re looking at more than 35,000 patients. Still, in 2018, less than one-third of patients with mCSPC received either docetaxel or abiraterone. This is unacceptable because these therapies, which are associated with dramatic improvements in OS, are not being offered to patients.

[In abstract 5072], which looked at more than 4000 patients and was a different data set, [information was] recruited from the Optum database, which include patient claim data from both commercially insured and Medicare Advantage populations. We are talking about patients well covered by insurance; one can argue that in a larger dataset, that many of these patients probably were not insured and probably couldn’t afford these drugs. [Still], we are looking at less than one-third of patients who are being treated with these drugs. Why does this happen?

Significant education and awareness are needed, and we need to solve this problem. [This shows an] unacceptable low use of life-prolonging therapy. All 3 studies point to a huge discordance between real-world practice and phase 3 trial results.”

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Real-world first-line (1L) treatment patterns in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) in a U.S. health insurance database (Abstract 5072);

Real-world utilization of advanced therapies and racial disparity among patients with metastatic castration-sensitive prostate cancer (mCSPC): A Medicare database analysis (Abstract 5073);

Real-world treatment patterns among patients diagnosed with metastatic castration-sensitive prostate cancer (mCSPC) in community oncology settings (Abstract 5074)

Each of the above 3 studies links to a common theme surrounding the real-world utilization of available therapies for patients metastatic castration-sensitive prostate cancer (mCSPC). In the first study, investigators assessed the use of effective combination therapies as first-line treatment in insured US patients with mCSPC. Their analysis showed that androgen deprivation monotherapy remained the predominant treatment choice (> 50%) in all tracked years and was the most frequently used therapy in patients with more aggressive disease.

In the Medicare database analysis, investigators evaluated the use of advanced therapies over time, providing data on utilization patterns among racial minorities that are often underrepresented in clinical trials. Over the study period (2010-2018), less than one-third of patients received treatment intensification and that there was less frequent treatment intensification among Black and non-Hispanic White patients, according to data.

Decreased fracture rate by mandating bone protection agents in the EORTC 1333/PEACE III trial combining Radium-223 with enzalutamide versus enzalutamide alone: An updated safety analysis (Abstract 5002)

In the updated safety analysis of PEACE III (NCT02194842), investigators confirmed the early fracture rates that had been observed when patients with mCRPC were treated with the addition of radium-223 dichloride (Xofogo) to enzalutamide in the absence of bone-protecting agents (BPA). At 1 year the fracture risk for patients without BPA who were treated with enzalutamide (n = 32) was 15.6%, and 37.1% for those who received enzalutamide plus radium-223 (n = 35).

At 1 year for patients with BPA the fracture risks were 2.6% for the enzalutamide arm (n = 97) and 2.7% for the combination arm (n = 87).

“A previous trial with abiraterone with radium-223, which showed an excessive incidence of fracture in the combination of abiraterone with radium-223, led to an amendment mandating the use of BPAs. What we saw was really remarkable. In the absence of bone-strengthening agents—for those who had already enrolled on the trial [before the mandate]—there was an increase in the risk of fracture when radium-223 was added to enzalutamide. Very strikingly, the risk was abolished by the use of BPAs. What
For HIGHER-RISK MDS

ISN’T IT TIME TO TRANSFORM SURVIVAL OUTCOMES?

Newly diagnosed patients with higher-risk myelodysplastic syndromes (HR-MDS) face poor outcomes

One class of agents is not enough—new options that can be used in combination with HMAs are urgently needed

~40% of patients transform to AML

12.4 months mOS in a real-world study

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*Observed in a real-world evaluation of a total 1101 adult patients, 825 with HR-MDS (defined by an IPSS score of intermediate-2 or high risk) and 276 with low-blast count AML (defined by 21-30% blasts) treated with azacitidine between 2010 and 2016 in Ontario, Canada. Transfusion dependence was determined by the Nordic Score definition of transfusion dependence: ≥2 units of blood transfused per 4 weeks.1

† Based on a 2018 review of transformation to secondary AML in MDS patients; as well as a 2016 multicenter, retrospective study of 7122 untreated MDS patients from 19 institutional databases. Risk of transforming to AML from HR-MDS was determined by IPSS and IPSS-R.2,3

AML=acute myeloid leukemia; HMAs=hypomethylating agents; HR-MDS=higher-risk myelodysplastic syndromes; IPSS=International Prognostic Scoring System; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndromes; mOS=median overall survival.

Ancestral characterization of the genomic landscape, comprehensive genomic profiling utilization, and treatment patterns may inform disparities in advanced prostate cancer: A large-scale analysis (Abstract 5003);
Association of increased intensity of prostate-specific antigen screening in younger African American men with improved prostate cancer outcomes (Abstract 5004).

The large-scale analysis (abstract 5003), which encompasses what may be the largest cohort of patients, defines the comprehensive genomic profiling utilization, genomic landscape, and treatment implications of this profiling in patients with advanced prostate cancer across ancestry.

Through the prostate-specific antigen (PSA) screening trial, investigators evaluated a large cohort of African American men aged 40 to 55 years. Findings showed that an increased intensity of PSA screening in this subgroup was linked with a reduction in the risk of lethal disease and metastases at diagnosis, as well as a decrease in prostate cancer-specific mortality.

“In 5003, African American men were less likely to receive tumor-comprehensive genomic profiling earlier in their treatment course and were less likely to be treated on clinical trials, which could impact the genomic landscape outcomes and ultimate disparities.

Finally, in the screening trial for African American men aged 40 to 55 years, data showed that an increased intensity of PSA screening was linked with a reduced risk of metastases at time of diagnosis and decreased prostate cancer-specific mortality, suggesting that PSA screening and early prostate cancer detection may improve outcomes for this patient population.”

Optimal treatment duration of bevacizumab (BEV) combined with carboplatin and paclitaxel in patients (pts) with primary epithelial ovarian (EOC), fallopian tube (FTC), or peritoneal cancer (PPC): A multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890) (Abstract 5501)

The optimal duration of bevacizumab (Avastin) when used in combination with chemotherapy in patients with primary epithelial ovarian, fallopian tube, or peritoneal cancer has remained unclear. In the BOOST trial (NCT01462890), results showed that treatment with the VEGFR inhibitor, when given up to 30 months, did not improve PFS or OS in this patient population. Specifically, the median PFS for patients treated with bevacizumab up to 30.0 months was 26.0 months (95% CI, 23.7-29.7) vs 24.2 months (95% CI, 22.2-26.5) with bevacizumab given up to 15 months (HR, 0.99; 95% CI, 0.85-1.15; log-rank P = .90). The median OS was 60.0 months (95% CI, 54.0-68.6) and 54.3 months (95% CI, 51.0-64.6), respectively (HR, 1.04; 95% CI, 0.87-1.23; log-rank P = .68).

The investigators concluded that 15 months of bevacizumab should remain the standard of care.

“Continuing on the theme from prior ASCO meetings, it would seem that more is not always better. The BOOST trial [results], presented by Dr Jacobus Pfisterer [of the AGO Study Group & Gynecologic Oncology Center in Kiel, Germany], revealed that additional cycles of frontline bevacizumab maintenance did not improve progression-free or overall survival in advanced-stage ovarian cancer.”

Maintenance vigil immunotherapy in newly diagnosed advanced ovarian cancer: Efficacy assessment of homologous recombination proficient (HRP) patients in the phase IIb VITAL trial (Abstract 5502)

Vigil immunotherapy (gemogenevatucel-T) is an autologous tumor cell vaccine comprising autologous harvested tumor tissue; it is transfected with a DNA plasmid encoding GMCSF and bi-shRNA-furin, which leads to control of TGF-β expression. Findings from the VITAL trial (NCT02346747) showed that, when given as a frontline maintenance treatment in patients with stage III/IV disease, Vigil is safe and has a statistically significant clinical benefit, including in those who are BRCA wild-type and homologous recombination proficient.

Updated survival data showed that in the all-comer population, patients treated with Vigil (n = 47) had a median OS of not reached vs 16.0 months with placebo (n = 44; HR, 0.63; P = .110). The median recurrence-free survival was 11.5 months with Vigil vs 8.4 months with placebo (HR, 0.68; P = .078), missing the primary end point.

The benefit was pronounced in patients with homologous recombination-proficient disease. For patients treated with Vigil (n = 25) the median OS was not reached compared with 26.9 months with placebo (n = 20; HR, 0.342; P = .019). The median recurrence-free survival for these patients was 10.6 months compared with 5.7 months with placebo (HR, 0.386; P = .007).

“Results from the [VITAL] study were quite exciting. The finding of improved recurrence-free and overall survival in women with [homologous recombination]-proficient ovarian cancer treated with the Vigil vaccine warrants further exploration in a randomized phase 3 study.”
**MULTIPLE MYELOMA**

Sagar Lonial, MD  
Winship Cancer Institute/Emory University School of Medicine  
Atlanta, GA

For part 2 of the Cassiopeia study (NCT02541383), investigators examined transplant-eligible patients with newly diagnosed multiple myeloma who received 4 cycles of induction treatment followed by 2 cycles of either daratumumab (Darzalex) plus bortezomib (Velcade), thalidomide (Thalomid), and dexamethasone (VTD) or VTd alone. Patients who received at least a partial response were rerandomized to daratumumab for up to 2 years or observation until disease progression. In the interim analysis, investigators looked at efficacy and safety following 281 PFS events.

Findings showed that maintenance treatment with daratumumab had a clinical benefit in this patient population compared with observation. At a median follow-up of 35.4 months from second randomization, the median PFS was not reached with daratumumab compared with 46.7 months with observation (HR, 0.53; 95% CI, 0.42-0.68; \( P < .0001 \)).

“While not the ideal design for a trial, it has the potential to help address if daratumumab offers benefit both with induction and maintenance. The suggestion that one only needs to see daratumumab either at induction or maintenance [phases] may be a very important result for patients and our community overall.”

In May the FDA granted a priority review to the biologics license application for ciltacabtagene autoleucel (cilt-a-cell) for patients with relapsed/refractory myeloma. The application used impressive response rate data from the phase 1/2 CARTITUDE-1 trial (NCT03548207) as support for the approval. Longer follow-up data showed that responses deepened with an increasing rate of stringent complete response. Specifically, the therapy elicited a 97.9% ORR among 97 patients when delivered at the recommended phase 2 dose (0.75 × 10^6 chimeric antigen receptor (CAR)-positive viable T cells/kg); this included an 80.4% stringent complete response rate.

Investigators noted that the median duration of response (DOR) was not reached in patients with stringent complete response and an estimated 73% of responders have not progressed or died at 12 months.

“Is there really a difference between BCMA [B-cell maturation antigen] CAR T-cell...”

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**Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by lenalidomide (R) or carfilzomib-lenalidomide (KR) maintenance: Efficacy in high-risk patients (Abstract 8002)**

Activity has previously been observed with KRd, the combination of carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone, followed by autologous stem cell transplant in patients with multiple myeloma, as seen in the FORTE trial (NCT02203643). This analysis of the pivotal study specifically looked at the effect this regimen had on high-risk and double-hit patients with myeloma. Results showcased its effectiveness in both of these subgroups, in addition to those with standard-risk disease vs 12 cycles of KRd alone.

For high-risk patients who went on to receive transplant (n = 80) the PFS rate was 62% compared with 45% for those who had KRd alone (n = 71; HR, 0.60; \( P = .04 \)). The PFS rate for patients with double-hit specifically looked at the effect this regimen had on high-risk and double-hit patients with myeloma. Results showcased its effectiveness in both of these subgroups, in addition to those with standard-risk disease vs 12 cycles of KRd alone.

High-risk patients who went on to receive transplant (n = 80) the PFS rate was 62% compared with 45% for those who had KRd alone (n = 71; HR, 0.60; \( P = .04 \)). The PFS rate for patients with double-hit specifically looked at the effect this regimen had on high-risk and double-hit patients with myeloma. Results showcased its effectiveness in both of these subgroups, in addition to those with standard-risk disease vs 12 cycles of KRd alone.

“[Treatment] of high-risk multiple myeloma is a challenge, and this trial helps support what many of us believe is important for improving PFS for these patients—the use of triplet induction, transplant, and IMiD/PI [immuno-modulatory imide drug/proteasome inhibitor] maintenance. This should help support a new standard of care for these patients.”

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**Daratumumab (DARA) maintenance or observation (OBS) after treatment with bortezomib, thalidomide and dexamethasone (VTD) with or without DARA and autologous stem cell transplant (ASCT) in patients (pts) with newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 2 (Abstract 8004)**

**Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1 (Abstract 8005)**

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**MORE ON OncLive.com**

**OncLive® News Network Unpacks 2021 ASCO Coverage from the virtual 2021 American Society of Clinical Oncology (ASCO) Annual Meeting** featured interviews with top experts about the most important research presented at the conference across tumor types. Putting the findings into perspective were Edward S. Kim, MD; Anthony R. Mato, MD; Erika P. Hamilton, MD; Milind Javle, MD; Nicholas J. Vogelzang, MD; Erin K. Crane, MD, MPH; Sandy Wong, MD; Neal Shore, MD; and Loretta Nastoupil, MD.

**Scan the QR code or go to bit.ly/2Uu4qFq**
products? Cila-tce investigators seem to think so. This dataset can help sort out if there are differences that impact outcomes broadly.*

Updated phase 1 results of teclistamab, a B-cell maturation antigen (BCMA) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM) (Abstract 8007)

Teclistamab has demonstrated activity in patients with relapsed/refractory multiple myeloma compared with other approved agents for those with triple-class exposed disease. Updated data from additional patients and longer follow-up showed that the recommended phase 2 dose of teclistamab (1500 µg/kg) was well tolerated and elicited an ORR of 65% among 40 treated patients. The agent had a reported very good response rate of 58% and a complete response rate of 40%; the median DOR was not reached. Moreover, the ORR in 33 triple-class refractory patients was 61%.

“CAR T-cell therapy vs bispecific is the question of the day in multiple myeloma. This study helps us understand the benefit in one of the largest data sets reported to date.”

Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM) (Abstract 8008)

The bispecific antibody talquetamab is another novel agent that demonstrated encouraging antitumor activity in the relapsed/refractory multiple myeloma population. At a median follow-up of 6.3 months, treatment with talquetamab resulted in a 70% ORR in 30 patients who had received the recommended phase 2 dose of 405 µg/kg delivered subcutaneously. Of note, 65.2% of patients with triple-refractory disease (15/23) and 83.3% of patients with penta-refractory disease (5/6) responded to talquetamab.

“Is there more than BCMA? Talquetamab data from this abstract say ‘yes!’ It is very exciting to have more than just CD38, SLAMF7, and BCMA as immune targets.”

IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC) (MM) (Abstract 8500)

Primary results of the IMpower010 trial (NCT02486718) demonstrated that adjuvant atezolizumab (Tecentriq) following adjuvant chemotherapy improved outcomes for patients with completely resected non-small cell lung cancer (NSCLC) vs best supportive care. The primary end point of disease-free survival (DFS) was met for patients with stage II-IIIA, PD-L1-positive disease (≥ 1% per SP263 assay). Specifically, the median DFS was not estimable (NE; 95% CI, 36.1-NE) for the 248 patients treated with atezolizumab compared with 35.3 months (95% CI, 29.0-NE) for the 228 patients treated with best supportive care (HR, 0.66; 95% CI, 0.50-0.88; P = .004).

Results were consistent in all-comers with a median DFS of 42.3 months (95% CI, 36.0-NE) vs 35.3 months (95% CI, 30.4-46.4) with atezolizumab and best supportive care, respectively (HR, 0.79; 95% CI, 0.64-0.96; P = .02).

“It was compelling. We all have this gut feeling that if we can do more, if we can do something more that has some benefit, we can help folks. We largely learned a lot of this from colon cancer and breast cancer that longer-term biologic-type therapy may help, and we see that in this study. This study will change how we approach lung cancer, especially in those patients with surgically resected [disease]—those patients who were treated with curative intent.

This study was a positive study, and it was even more so profound in the PD-L1 [subgroup] where the [CPS] was greater than 1%...Overall survival is still immature, so it is going to take a little longer this is what we have to wait for when we treat patients early in the curative setting. I anticipate this study will change how we approach [treatment for] patients with early-stage resectable NSCLC.”

Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC) (Abstract 8503)

Surgical outcome data from the randomized phase 3 CheckMate 816 trial (NCT02998528) seem to support the role of nivolumab (Opdivo) in combination with chemotherapy as a potential neoadjuvant option for patients with resectable NSCLC. The addition of the nivolumab significantly improved pathologic complete response (pCR) compared with chemotherapy alone in patients regardless of disease stage. Specifically, the pCR rates were 40% vs 0%, respectively, in patients with stage IB disease; 23% vs 3% for those with stage IIA disease; 24% vs 9% for those with stage IIB disease; and 23% vs 1% for those with stage IIIA disease. Further, the median residual viable tumor percentages (≤ 10%) were 28% vs 79% for nivolumab and chemotherapy alone, respectively, in patients with stage IB/II disease and 8% vs 70% for those with stage IIIA disease.

Some of the interesting observations that [the investigators included] was that the number of patients who underwent definitive surgery was higher in the nivolumab treated arm than those who just got chemotherapy. Remember there is not a placebo here, it is a treatment vs a treatment plus immunotherapy...[Investigators also noted that] residual viable tumor was very low, it was 10% vs 74%.”
Advancing Care in Metastatic Breast Cancer

AS THE MOST COMMONLY diagnosed type of cancer, the devastating effects of breast cancer continue to impact families around the world.\(^1\) It’s the fifth most frequent cause of cancer deaths globally, resulting in an estimated 685,000 deaths in 2020 alone, and a physical and emotional burden for patients and their caregivers.\(^2\)

Approximately 75% of breast cancers are classified as estrogen receptor-positive (ER+),\(^3\) making it the most common type of the disease diagnosed today.\(^4\) In ER+ breast cancers, cancer cells in the body are fueled by a person’s own estrogen hormones,\(^5\) and because women and men both produce estrogen,\(^6\) both could be at risk for potentially developing ER+ breast cancer.

Metastatic breast cancer (MBC) refers to cancer that has spread outside the breast to another part of the body, such as the liver, brain, bones or lungs.\(^7\) Also known as Stage IV, this is considered the most advanced stage of breast cancer.\(^7\) In the U.S., between 20%-30% of patients initially diagnosed with earlier stages of breast cancer eventually develop recurrent advanced or metastatic forms of the disease.\(^8\) Sadly, the five-year relative survival rate for metastatic female breast cancer is only 28%.\(^9\)

UNMET NEEDS IN MBC TREATMENT

There is currently no cure for MBC. Breast cancer cells adapt to their environment and mutate, which leads to drug resistance and disease progression over time.\(^3\) Once a person reaches the metastatic stage of breast cancer, each subsequent treatment line tends to be effective for a shorter duration than the previous line of therapy due to increasing cancer resistance.\(^9\) This commonly occurs in ER+ breast cancer.\(^11\)

Most endocrine therapies inhibit tumor growth by either lowering estrogen levels or blocking the estrogen from activating the estrogen receptors.\(^12\) First-line therapy for ER+ MBC often includes anti-estrogen therapies, or endocrine therapies, in combination with cyclin-dependent kinase (CDK) 4/6 inhibitors.\(^13\) The clinical use of CDK4/6 inhibitors has significantly improved the prognosis of patients with hormone-receptor positive (HR+) human epidermal growth factor receptor 2 (HER2)-negative MBC.\(^14\) While these therapies are often effective early in the course of the disease, approximately 30%-50% of people treated for ER+ breast cancer develop resistance to endocrine therapies.\(^13\) When cancer cells become resistant to therapy and progress, patients require multiple treatment approaches over time.\(^15\)

Given the complex nature of MBC, there is an urgent need for new therapies and novel ways to overcome drug resistance. Recognizing the need for new solutions, our researchers at Sanofi are investigating an approach to treating ER+ breast cancer that aims to combine estrogen receptor (ER) binding potency with an oral administration. This approach involves antagonizing and degrading the ER, resulting in inhibition of the ER signaling pathway.

COMMITMENT TO RESPONSIVE INNOVATION IN MBC

As we advance these research efforts on behalf of people living with breast cancer, we’re keenly aware of the equally important task of addressing unmet needs that go beyond treatment. While early-stage breast cancer is often a story of hope, recent surveys of women living with MBC found that more than 85% do not feel included in the “pink ribbon” breast cancer initiatives, underscoring the need for more recognition and support for those in later stages of illness.\(^16\)

Over the years, healthcare providers have also expressed frustration over the significant unmet needs in breast cancer. The MBC community has voiced its collective desire for new treatment options and a better balance between potential effectiveness and impacts on quality of life.\(^17\)

At Sanofi, we understand that an MBC diagnosis is a very different experience than early-stage breast cancer, and we are committed to actively working with the community to drive awareness of the realities of living with this challenging disease over its entire spectrum. Every person’s experience is unique, and our clinical research programs are designed to reflect the diverse patient populations that diseases affect. Our clinical research program in MBC, for example, was informed by eight panels and interviews involving 40 patients with diverse backgrounds.

Until we have a cure, we will continue to work toward advancing care – addressing the real needs of people living with MBC by balancing the potential for extending survival with the effects on a person’s ability to function and maintain their quality of life. ■
Clinical Trial In Focus | NSCLC

Investigators Explore the Role of VS-6766 and Defactinib in KRAS-Mutant NSCLC

by KYLE DOHERTY

PATIENTS WITH NON–SMALL CELL lung cancer (NSCLC) harboring KRAS mutations have been an underserved population with few treatment options, specifically those with G12V mutations. Investigators hope to build on early efficacy data in this patient population with a novel combination approach and address this unmet need with the commencement of the phase 2 RAMP 202 trial (NCT04620330).

RAMP 202 will evaluate the safety and efficacy of VS-6766, a RAF/MEK inhibitor, alone and in combination with defactinib, a FAK inhibitor, in adult patients with KRAS-mutant NSCLC following treatment with an appropriate platinum-based regimen and an approved immune checkpoint inhibitor.1

FINDING THE CORRECT ROADBLOCKS FOR KRAS

Approximately 30% of patients with NSCLC harbor a KRAS mutation, and agents targeting various components of the RAS pathway have met hurdles. For example, MEK inhibitors have been limited in their ability to impede ERK signaling because of possible feedback reactivation of RAF, which results in MEK phosphorylation.2 Investigators have determined that the bypassing mechanisms and resistance in the blockade of the RAS pathway may be circumvented through the inhibition of parallel pathways in the extracellular matrix, namely the FAK-signaling pathway.3

“There’s a signaling pathway that is partially in a straight line that goes RAS, RAF, MEK, ERK,” explained D. Ross Camidge, MD, PhD, a professor of medicine and medical oncology, director of the Thoracic Oncology and Clinical Research Programs at the University of Colorado (CU) School of Medicine, and CU Cancer Center member in Aurora, in an interview with OncologyLive®.

“The pathway is commonly used by many different cancers and it’s so important to some cancers that there are often mutations in that pathway. We know there were some cancers driven by BRAF mutations and ARAF mutations [and] we know there are some cancers driven by RAS mutations. ‘One of the problems is that it’s a bit like a tree; lots of these branches come off at each of these points. The question is how do you shut down signaling without some bypass loop going around it. VS-6766 is hitting it at 2 separate points, hitting it at the RAF level and at the MEK level.”

The investigational agent VS-6766 blocks MEK kinase activity and also prevents the process of RAF to phosphorylate MEK. The mechanism of VS-6766 allows for more effective inhibition of ERK signaling and may lead to greater therapeutic activity against ERK-dependent RAS- or BRAF-mutant tumors. In preclinical models, the agent showed synergy with G12C inhibitors in KRAS-mutant NSCLC and colorectal cancer. In mouse models, VS-6766 has also demonstrated the ability to enhance the antitumor effects of PD-1–targeted therapies in KRAS-mutant NSCLC.4

Further, VS-6766 has demonstrated significant tumor regression in KRAS G12V-mutant NSCLC, one of the second most common codon 12 variants identified with

FIGURE. Study of Dual RAK/MEK Inhibitor as a Single Agent and in Combination With FAK Inhibitor in Patients With Recurrent KRAS-Mutant NSCLC

Phase 2 (NCT04620330)

Eligibility criteria
• Prior appropriate treatment with a platinum-based regimen and immune checkpoint inhibitor
• Age ≥ 18 years
• Measurable disease according to RECIST v1.1 criteria
• ECOG performance status ≤ 1
• Adequate organ function
• Adequate recovery from toxicities related to prior treatments

Selection phase
Defactinib+VS-6766* KRAS G12V-mutant cohort
VS-6766* KRAS G12V-mutant cohort
Defactinib+VS-6766* Nonmutant cohort

Expansion phase
KRAS G12V-mutant cohort
Selected regimen based on ORR
Nonmutant cohort
Exploratory mutation-specific cohort analyses for ORR

End points
Primary
• To determine the optimal regimen, either VS-6766 monotherapy or VS-6766 in combination with defactinib

Select secondary
• ORR
• DOR
• DCR
• PFS
• OS

DCR, disease control rate; DOR, duration of response; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

*Defactinib 200 mg orally, twice daily [21/28 days] + VS-6766 3.2 mg orally, twice daily, 2 times per week [21/28 days]

**VS-6766 4.0 mg orally, twice daily, 2 times per week [21/28 days]
**Clinical Trial In Focus**

**NSCLC**

**KRAS.** KRAS G12V–mutant disease has been shown to be more reliant on CRAF, and preclinical models have shown that CRAF ablation with VS-6766 improved the survival of mice with mutant disease over BRAF ablation in vivo. 3

Defactinib, an oral small molecule inhibitor of FAK and PYK2, promoted stronger tumor regression when combined with VS-6766, according to results from in vivo models. 5 The agent has been granted an orphan drug designation for the treatment of patients with ovarian cancer and mesothelioma in the United States, the European Union, and Australia. Preclinical models of KRAS-mutant solid tumors treated with defactinib and VS-6766 show the combination to be synergistic in several KRAS-mutant tumor cell lines. 6

**INITIAL SAFETY AND EFFICACY DATA OF VS-6766 AND DEFACTINIB**

The combination of VS-6766 and defactinib is currently under investigation in the phase 1/2 FRAME study (NCT03875820), a basket trial enrolling patients with solid tumors with KRAS mutations. Patient populations include those with low-grade serous ovarian cancer, KRAS-mutant NSCLC, and KRAS-mutant colorectal cancer.

In FRAME, VS-6766 and defactinib were administered using a twice-weekly and twice-daily dose-escalation schedule, respectively, in week 3 of a 4-week cycle. Investigators determined the recommended dose for phase 2 of the study as being VS-6766 3.2 mg and defactinib 200 mg. 7

Preliminary results showed the combination displayed activity in patients with KRAS-mutant NSCLC included in the study analysis (n = 10). Patients were refractory to conventional treatment or had no conventional treatment options available to them; they had received a median of 2 prior lines of therapy and a majority had prior anti–PD-1 therapy. An analysis showed that 1 patient experienced a partial response and 8 patients achieved disease control. Patients in this cohort continued on treatment for at least 12 weeks at a rate of 70%, and 30% continued on treatment for at least 24 weeks. Of note, the patient who achieved a partial response had KRAS G12V-mutant disease and remained on therapy for more than 3 months. 7

In a subsequent combined analysis of the FRAME study and a prior VS-6766 single-agent study, patients with NSCLC harboring the specific KRAS G12V mutation (n = 7) experienced an overall response rate (ORR) of 57% when treated with VS-6766 either as a single agent or in combination with defactinib.

The most common adverse events observed in FRAME, most of which were grade 1 or 2, were rash, creatine kinase elevation, nausea, hyperbilirubinemia and diarrhea. 4

"[Verastem Oncology did] a study which combined the drug with a FAK inhibitor, and also [examined it] as a monotherapy," Camidge said. "In that dose-escalation, dose-expansion study, there were a number of patients with a specific KRAS mutation called KRAS G12V, who mostly all had ovarian cancer. They responded. Some of them responded to the combination and some of them responded to monotherapy, so we don’t know whether you actually need the combination. I saw the data and G12V is also present in NSCLC. I reached out to them and said, ‘You know, you should really also develop this in lung cancer.’ That’s what led to the RAMP 202 study.”

**DETAILS OF THE RAMP 202 TRIAL**

RAMP 202 is a multicenter, parallel cohort, randomized, open-label trial that will enroll approximately 100 patients in the United States and the European Union. In part 1 of this adaptive 2-part study, investigators will determine the optimal regimen of VS-6766 either as a monotherapy or in combination with defactinib, with patients randomized 1:1 in each arm. Once they have determined the optimal regimen, the investigators will evaluate the safety and efficacy in part 2. 7

To be eligible for the trial, patients must be at least 18 years old with histologic or cytologic evidence of NSCLC, have a known KRAS mutation, and have received appropriate prior therapy. Participants must have an ECOG performance status of at least 1, adequate organ function, and adequate recovery from toxicities related to prior treatments. 8

The primary end points of the study are to determine the optimal regimen and to determine the efficacy of the optimal regimen. Secondary end points include ORR as assessed by the investigator, duration of response, disease control rate, progression-free survival, and overall survival. 8

“If we see reproducible, robust, and durable responses in KRAS G12V, or other subtypes, it certainly puts a target on the back of G12V as something that could lead to regulatory approval of this specific approach for that specific mutation,” Camidge said. "If it shows more modest activity, that still opens up the idea that this could be an ingredient that could be combined with other drugs. We have some leads in ovarian cancer, but we have to prove it in lung cancer.”

**REFERENCES**


Neoadjuvant Cemiplimab Elicits Complete Pathological Responses in HCC

by COURTNEY MARABELLA

**significant tumor necrosis was observed** in 20% of patients with resectable hepatocellular carcinoma (HCC) who received neoadjuvant treatment with cemiplimab-rwlc (Libtayo), according to data from an open-label, multicohort phase 2a study (NCT03916627) presented during the American Association for Cancer Research Annual Meeting 2021. Significant tumor necrosis, defined as greater than 70% necrosis of the resected tumor, was reported in 4 of 20 patients following treatment with neoadjuvant cemiplimab, meeting the primary end point of the study. Additionally, 15% of patients (n = 3/20) achieved complete tumor necrosis of 100%, whereas 35% of patients (n = 7/20) had tumor necrosis of at least 50.

“The pathological response data support larger trials to identify optimal clinical end points that correlate with improvement in survival and to establish the utility and safety of peroperative PD-1 in patients with resectable HCC,” said lead study author Thomas Urban Marron, MD, PhD, the assistant director of immunotherapy and early phase trials at The Tisch Cancer Institute, and an assistant professor of medicine, hematology and medical oncology, at the Icahn School of Medicine at Mount Sinai in New York, New York.

For patients with early-stage HCC, the recommended first-line treatment is surgery. Although negative margins are often observed at the time of resection, most tumors recur. It is hypothesized that disease recurrence is a result of micrometastases that persist after surgery. Neoadjuvant therapy could potentially improve outcomes for patients with HCC, although there is no standard recommended treatment in this setting.

Cemiplimab is an IgG4 monoclonal anti-PD-1 agent approved by the FDA for select patients with advanced cutaneous squamous cell carcinoma, as well as for select patients with advanced or metastatic basal cell carcinoma, and for patients with non–small cell lung cancer (NSCLC) who have a PD-L1 expression of 50% or higher. In the phase 2a study, investigators sought to examine the clinical activity of the agent in patients with resectable HCC.

To be eligible for enrollment, patients had to be 18 years of age or older, have an ECOG performance status of 0 or 1, and acceptable organ function. Those who had received prior cancer treatment within 6 months before entering the study or who had undergone major surgery within 14 days of starting neoadjuvant treatment were excluded. Additionally, individuals with metastatic disease for whom surgery would not be curative were not eligible.

Patients with HCC who were candidates for surgical resection were treated with neoadjuvant cemiplimab intravenously at a dose of 350 mg every 3 weeks for 2 cycles prior to surgery. Following the procedure, patients were treated with the same dosing regimen for an additional 8 cycles.

“Before treatment, patients underwent 3-dimensional MRI imaging and core needle biopsies of their tumor,” Marron noted. "Blood was collected throughout the perioperative period, and patients underwent repeat imaging immediately before surgical resection.”

The primary end point of the study was significant tumor necrosis, based on pathological analysis of gross tumor resection at the time of surgery. Secondary end points included delay of surgery, disease-free survival, overall response rate per modified RECIST v1.1 criteria, overall survival, adverse effects, and change in lymphocyte infiltration.

Among the 21 patients initially enrolled to the study, the median age was 68 years (range, 45-82), and 85.7% were male. Additionally, 52.4% were of Asian descent and 85.7% had an ECOG performance status of 0. Patients received a median duration of 6 weeks (range, 5.3-6.7) of neoadjuvant treatment. One patient was found to have metastatic disease upon surgery and resection was canceled.

Additionally, pathological assessments of change in necrosis and tumor-infiltrating CD8 T-cell density from baseline were conducted in both pretreatment biopsies and resected tumor samples following neoadjuvant treatment. Resected tumor samples were processed for tumor DNA, multiplex ion beam imaging, immunohistochemistry assays, mutational analysis, and single-cell biomarker analysis.

Initial pathological assessments demonstrated a potential association between immune cell infiltration and tumor necrosis. Multiplex immunohistochemistry and single-cell tissue and blood analysis are ongoing.

In terms of safety, 90.5% of patients (n = 19/20) experienced at least 1 treatment-emergent adverse effect (TEAE) of any grade, and 28.6% (n = 6) of patients experienced a grade 3 or higher TEAE.

One patient experienced grade 3 pneumonia while receiving neoadjuvant treatment with cemiplimab, which resulted in a surgery delay of 2 weeks per the protocol-defined surgical window. Once the TEAE was resolved, the patient underwent surgery.

**Table.** Efficacy Data From NCT03916627

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cemiplimab (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis &gt; 70%</td>
<td>20%</td>
</tr>
<tr>
<td>Complete tumor necrosis</td>
<td>15%</td>
</tr>
<tr>
<td>Tumor necrosis ≥ 50%</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Reference**

INDICATIONS & USAGE
MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

For NTE adult patients with DLBCL who have received at least 1 prior therapy

REACH TO SECURE A RESPONSE'

IMPORTANT SAFETY INFORMATION
Contraindications
None.

Warnings and Precautions
Infusion-Related Reactions
MONJUVI can cause infusion-related reactions (IRRs). In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication.

Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.
MONJUVI®
tafasitamab-cxix | 200mg
for injection, for intravenous use

INDICATIONS & USAGE
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend tafasitamab-cxix (MONJUVI) in combination with lenalidomide as a second-line or subsequent therapy option for DLBCL in patients who are not candidates for transplant.2

It is unclear if tafasitamab will have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

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

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor complete blood counts (CBC) prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony-stimulating factor (G-CSF) administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

IMPORTANT SAFETY INFORMATION
Warnings and Precautions (cont’d)
SECURE RESPONSE IN SECOND LINE

MONJUVI is the first and only FDA-approved treatment for adult patients with DLBCL who have received at least 1 prior therapy, in combination with lenalidomide

High ORR reached, with a majority of responders achieving CR

Best overall response rate in patients with R/R DLBCL (N=71)

- 37% CR
- 55% ORR (n=39; 95% CI: 43%, 67%)
- 18% PR

Response sustained beyond 18 months

Duration of response in patients with R/R DLBCL (n=71)

- Median DoR: 21.7 months
- (range: 0, 24)

L-MIND study design

- L-MIND was an open-label, multicenter, single-arm study that evaluated the efficacy and safety of MONJUVI in combination with lenalidomide followed by MONJUVI monotherapy in adult patients with R/R DLBCL after 1 to 3 prior systemic DLBCL therapies, including CD20-containing therapy. The median number of prior therapies was 2
- Enrolled patients at the time of the trial were not eligible for or refused ASCT
- Efficacy was established in 71 patients with DLBCL (confirmed by central laboratory) based on best ORR (defined as the proportion of complete and partial responders) and DoR, as assessed by an Independent Review Committee using the International Working Group Response Criteria (Cheson 2007)
- Patients received MONJUVI 12 mg/kg intravenously in combination with lenalidomide (25 mg orally on days 1 to 21 of each 28-day cycle) for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity

NCCN = National Comprehensive Cancer Network; ORR = overall response rate; CR = complete response rate; R/R = relapsed/refractory; PR = partial response rate; CI = confidence interval; DoR = duration of response; ASCT = autologous stem cell transplant.

*Assessed by an Independent Review Committee.
**SECURE RESPONSE IN SECOND LINE**

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**INDICATIONS & USAGE**

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**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions (cont’d)**

**Embryo-Fetal Toxicity**

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose. MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

**Adverse Reactions**

Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥6% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions (≥20%) were neutropenia (51%), fatigue (38%), anemia (36%), diarrhea (36%), thrombocytopenia (31%), cough (26%), pyrexia (24%), peripheral edema (24%), respiratory tract infection (24%), and decreased appetite (22%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to MORPHOSYS US INC. at (844) 667-1992.

▶ To learn more, visit [MonjuviHCP.com](http://MonjuviHCP.com)
▶ For information about patient assistance, visit [MyMissionSupport.com](http://MyMissionSupport.com)

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

**REFERENCES:** 1. MONJUVI Prescribing Information. Boston, MA: MorphoSys. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V.4.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 24, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
MONJUVI® (tafasitamab-cxix)
Initial U.S. Approval: 2020

INDICATIONS AND USAGE
MONJUVI, in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
MONJUVI can cause infusion-related reactions. In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication.

Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12%, and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor CBC prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony-stimulating factor administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections
Fatal and/or serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Embryo-Fetal Toxicity
Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
The safety of MONJUVI was evaluated in L-MIND. Patients (n=81) received MONJUVI 12 mg/kg intravenously in combination with lenalidomide for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Among patients who received MONJUVI, 57% were exposed for 6 months or longer, 42% were exposed for greater than one year, and 24% were exposed for greater than two years.

Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥2% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions (≥20%) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

Table 3 summarizes the adverse reactions in L-MIND.

Table 3: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>3.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>1.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>1.2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection†</td>
<td>24</td>
<td>4.9</td>
</tr>
<tr>
<td>Urinary tract infection‡</td>
<td>17</td>
<td>4.9</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>1.2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>19</td>
<td>2.5</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

†Fatigue includes asthenia and fatigue
‡Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection

Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal

Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:
- Blood and lymphatic system disorders: lymphopenia (6%)
- General disorders and administration site conditions: infusion-related reaction (6%)
- Infections: sepsis (4.9%)
- Investigations: weight decreased (4.9%)
- Musculoskeletal and connective tissue disorders: arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- Neoplasms benign, malignant and unspecified: basal cell carcinoma (1.2%)
- Nervous system disorders: headache (5%), paresthesia (7%), dysesthesia (8%)
- Respiratory, thoracic and mediastinal disorders: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- Skin and subcutaneous tissue disorders: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)
Table 4 summarizes the laboratory abnormalities in L-MIND.

### Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time increased</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

The denominator used to calculate the rate was 74 based on the number of patients with a baseline value and at least one post-treatment value.

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assays. 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 tafasitamab products may be misleading.

Overall, no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety profile of tafasitamab-cxix were observed in 2.5% of 81 patients with relapsed or refractory DLBCL with pre-existing anti-tafasitamab antibodies in L-MIND.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. There are no available data on MONJUVI use in pregnant women to evaluate for a drug-associated risk. Animal reproductive toxicity studies have not been conducted with tafasitamab-cxix.

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.

MONJUVI is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide prescribing information for additional information. Lenalidomide is only available through a REMS program.

**Clinical Considerations**

**Fetal/Neonatal Adverse Reactions**

Immunoglobulin G (IgG) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, MONJUVI may cause depletion of fetal CD19 positive immune cells. Defer administering live vaccines to neonates and infants exposed to tafasitamab-cxix in utero until a hematology evaluation is completed.

**Data**

**Animal Data**

Animal reproductive studies have not been conducted with tafasitamab-cxix. Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

**Lactation**

**Risk Summary**

There are no data on the presence of tafasitamab-cxix in human milk or the effects on the breastfed child or milk production. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to MONJUVI are unknown. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose. Refer to lenalidomide prescribing information for additional information.

**Females and Males of Reproductive Potential**

MONJUVI can cause fetal B-cell depletion when administered to a pregnant woman.

**Pregnancy Testing**

Refer to the prescribing information for lenalidomide for pregnancy testing requirements prior to initiating the combination of MONJUVI with lenalidomide.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose. Additionally, refer to the lenalidomide prescribing information for additional recommendations for contraception.

**Males**

Refer to the lenalidomide prescribing information for recommendations.

**Pediatric Use**

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

**Geriatric Use**

Among 81 patients who received MONJUVI and lenalidomide in L-MIND, 72% were 65 years and older, while 38% were 75 years and older. Clinical studies of MONJUVI did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs compared to that of younger subjects. Patients 65 years and older had more serious adverse reactions (57%) than younger patients (39%).

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full Prescribing Information.
Advanced Practice Providers Are Poised to Boost Community Involvement in Clinical Trials

by ERIN M. BURNS, PhD

INvolvement in Clinical Trials

and referrals for patient enrollment are factored into the standard regimen of care for oncology advanced care providers (APPs) associated with academic centers and large cancer institutions. However, for those in the community setting several barriers to clinical research prevent APPs and their patients from taking part in experimental therapies.1

According to data from the American Society of Clinical Oncology’s (ASCO) annual Practice Census, the number of oncology practices in the United States that have reported employing APPs increased from 52% in 2014 to 81% in 2017.2,3 A collaborative effort of ASCO, the American Academy of Physician Assistants, the Association of Physician Assistants in Oncology, the Advanced Practitioner Society of Hematology and Oncology, and the Oncology Nursing Society led to the identification of 5350 oncology APPs practicing in the United States, with the possibility of that number being close to approximately 7000.

APPs are involved in various aspects of care including roles as nurse practitioners (NPs), physician assistants (PAs), and other licensed, nonphysician providers such as clinical nurse specialists, certified nurse midwives, and certified registered nurse anesthetists.2 NPs are regulated and licensed by state nursing boards, although requirements for recertification and continuing education vary.4

Furthermore, approximately half of states authorize NPs to independently practice without the need for oversight,3,4 and all states grant full prescriptive authority for NPs.5 Additionally, PAs are also regulated by state medical boards and must practice with a supervising physician, with extent of physician supervision varying by state.6,7 PAs are able to write prescriptions in all states.8

Apps in Clinical Trials

APPs associated with institutions often fill roles in clinical trials as primary investigators (PIs), subinvestigators, study coordinators, and/or in the delivery and monitoring of therapies for patients. Results from a 65-item survey of attitudes, beliefs, and roles of oncology APPs in clinical research that was distributed via the Association of Community Cancer Centers (ACCC) demonstrated that oncology APPs are engaged and interested in clinical trials, and believe clinical research is important to improve care. However, they may not be used to their full scope.9

Barriers include a lack of time, inadequate awareness of clinical trials, and underrepresentation on research committees. Recommendations for realizing the potential of APPs include research-related education, more complete integration as a member of the multidisciplinary cancer care team, and federal and state policy and regulatory changes.

“I work with 1 other oncologist, and we keep a portfolio of our available trials,” Christa Braun-Inglis, MS, APRN, FNP-BC, AOCN, of the University of Hawaii Cancer Center in Honolulu, told OncologyLive®. “I’ll see a patient for treatment counseling, and I’ll assess whether or not [a patient] is eligible for either a treatment trial or symptom management trial that we have available. [The oncologist and I] have this workflow where she will introduce the trial during the consult and then I’ll pick up from there during the treatment counseling, and I will decide whether or not they are eligible and interested in enrolling in the trial.”

Braun-Inglis, who is the primary author of the study and an oncology NP, emphasized that her experience with clinical trials and clinical research has been in the community setting at the University of Hawaii Cancer Center. She explained that she functions within the National Cancer Institute (NCI)-sponsored Community Oncology Research Program, where she is PI on several quality-of-life, symptom-control cancer care delivery protocols. She also noted that she provides clinical support to the research coordinators.

Laura J. Zitella, MS, RN, ACNP-BC, AOCN, of the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, said she works at an academic...
medical center with a very robust clinical trials program. “My primary role is the clinical care of patients, and in that role I take care of patients who are receiving standard-of-care treatments,” Zitella said. “But I also take care of patients who are enrolled in clinical trials. I am a subinvestigator on clinical trials that are related to the patient population that I care for.”

Zitella, a hematology/oncology NP, said she includes clinical trials in treatment discussions with patients and communicates with the primary trial investigator and the clinical research coordinator to enroll patients in trials. “I am involved with consenting and performing research procedures, and ordering study drugs, and all of the other processes that go along with being [enrolled in] a clinical trial,” she said. “It’s very common for APPs at academic medical centers to be involved with clinical research and to be subinvestigators on clinical trials for the patient population that they take care of.”

Lisa A. Kottschade, MSN, APRN, CNP, an NP at Mayo Clinic in Rochester, Minnesota, said, “Oncology APPs can play a number of roles in clinical research. Some things that come to mind include patient recruitment and management on clinical trials [or] serving as principal investigators on certain trials and coinvestigators. Additionally, APPs can participate in NCI cooperative groups and institutional research committees. I belong to our cancer center’s scientific review committee and our data safety monitoring board.”

**CURRENT CHALLENGES FOR APPs**

In the community setting, Braun-Inglis noted that very few APPs are enrolling their patients in trials even though they can do so for trials in the symptom management/quality-of-life cancer care delivery space. Based on the survey findings, over 70% of APPs would like to have a larger role in clinical research (FIGURE 2,9). “I want us to really participate to the extent that our licensure, our scope, and our role within our institutions will allow,” she said.

Braun-Inglis also emphasized that there is
no formal training available for APPs at this time, but access to initiatives could be beneficial in 4 areas:

- How to assess a patient for a trial in everyday practice
- How to become a good investigator and follow good clinical practice
- How to review a study protocol for feasibility and scientific integrity
- How to play a role in protocol development and leadership

This year, the Advanced Practitioner Society for Hematology and Oncology (APSHO) launched a research and quality task force to identify needs within the APP community, with a goal to develop curriculum that APPs can access. “We still see only 3% to 5% of adult oncology patients going on trials,” Braun-Inglis said. “Here we are, a group of health care providers that has grown exponentially in the last 10 years. We’re not being routinely engaged in this process. I think the interest is there; now [the question is] how do I do this at my practice?”

Zitella noted that an area of opportunity for oncology APPs is to be educated and aware of clinical trials and to be able to discuss them as a potential treatment option for patients. “There are a number of organizations trying to increase awareness and education about clinical trials for APPs, including APSHO and ACCC,” she said. “I think that if people are involved with professional organizations, go to meetings and network with other oncology APPs, and hear about what other people are doing...that makes a difference.”

**APPs CAN SHAPE THE FUTURE OF CLINICAL TRIALS**

Currently, APPs are not able to order drugs or treatments for Cancer Therapy Evaluation Program (CTEP)-sponsored trials or any drug that holds an investigational new drug application, all of which contribute to a substantial barrier in practice.

In September 2020, the NCI developed a guideline that allows APPs to sign for drugs for nontreatment trials. “Even though there is that guideline that exists now, it’s still fuzzy,” Braun-Inglis explained. “You meet barrier after barrier. Our whole platform is to allow us to practice at the top of our licensure and scope within the realm of trials and not have the trial or the sponsor of the trial limit our practice. I’m hoping in the next couple of years or even a year that we’re going to see the changes come from the CTEP-sponsored trials. My real push is to make APPs leaders for other trials because we do all those things every day. There is no reason that we shouldn’t have a significant amount of involvement.”

Zitella said there has been a significant shift in the last year because the NCI clarified some of the responsibilities of nonphysician investigators. “All cooperative groups now have nursing committees, and I think that we are going to see more progress in integrating APPs into those roles,” Zitella said. “I think the other area where we’re going to see a lot of progress is integrating the patient; this is a key element for the future of clinical trial design. Academic medical centers, professional organizations, cooperative groups, and the NCI are really trying to partner with community oncology practices to make it easier and more feasible to conduct clinical research and to have them be a part of clinical trials.”

Kottschade noted that clinical trials in oncology are often the best option for patients for treatment, and in some cases, the only option and that APPs will affect the extent to which clinical trials are leveraged in the community setting. “The use of APPs in the community setting will expand access for patients to be enrolled on clinical trials, through increased awareness, education, and access,” she said.

Braun-Inglis added, “I would love for APPs to take a look at their practice, look at the clinical research available in their practice, and really evaluate [how they can be] practicing at the top of their scope and licensure.”

Zitella emphasized the importance of always considering clinical trials as treatment options. “Even if you don’t work in clinical trials, being aware of them, knowing where to find them and feeling comfortable discussing them with patients, is really important because patients are relying on us for our opinion and for our knowledge,” she said.

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**Medical Economics**

**How to Keep Getting Paid for Telehealth in 2021**

_by TERRI JOY_

**THE FLOURISHING OF TELEHEALTH** in 2020 was driven not just by necessity, but also by a significant loosening of governmental regulations and of reimbursement requirements by payers. Today, states and payers are rapidly changing their rules and laws rapidly. A good first step for many practices is to wean themselves away from noncompliant communications to immediate implementation of a Health Insurance Portability and Accountability Act–compliant telehealth solution, which will be essential when the public health emergency is terminated.

Here are 3 best practices to ensure that you will continue to be paid for your telehealth services.

1. Check to see if your state has proposed or passed legislation requiring insurance companies to cover telehealth.
2. Closely monitor bulletins and announcements regarding telehealth from any insurance payers that your practice accepts.
3. Update and clarify your practice’s financial policy regarding collection of copays for telehealth services.

TO READ THE FULL ARTICLE, VISIT: bit.ly/2T1rbFm

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For a full list of references, see the article at OncLive.com.
Community-Based Programs Have the Power to Remove Clinical Trial Barriers

by KHALID MATIN, MD, FACP

FOR DECADES, THERE HAS been a persistent lack of diversity among cancer-related clinical trial participants. This disparity affects both the patients and the science. A community-based approach to cancer care and research could offer a solution.

Though homogeneity is not unique to cancer trials, it is especially troubling to see it in the context of patients with cancer because clinical trials offer a means to access the newest and most promising treatments, such as immunotherapy. Further, profiles of disease are diverse and vary across gender, race/ethnicity, and other patient characteristics. Homogeneous trials present a missed opportunity to discover treatments that might be highly successful in a particular subset of patients.

UNDERREPRESENTATION SPANS RACE, LOCATION, AND AGE

In an analysis of phase 3 cancer-related clinical trials conducted between 2001 and 2010, results showed that 83% of participants were White, 6% were Black, 3% were Asian, 2% were Hispanic, and less than 1% were Native American. These results skewed heavily White compared with the overall racial demographics of cancer incidence in the United States.

Despite efforts to increase diversity in clinical trials, such as the National Institutes of Health (NIH) Revitalization Act of 1993, which required the inclusion of more women and individuals of color in trials funded by the NIH, diversity of among participants enrolled in oncology trials decreased in the 2000s, compared with the previous decade.

That is troubling because we know from other fields of study that the efficacy of certain drugs for patients in one racial or ethnic group do not necessarily generalize to others, or they may have unforeseen adverse effects among minority groups that were not adequately represented during the testing phase. Currently, Black patients with cancer have a 28% higher mortality rate compared with White patients, and if the standard of care continues to be defined using predominantly White volunteers this inequity in cancer outcomes will persist.

One reason for the lack of racial and ethnic diversity in oncology trials is the not-so-distant memory of abuse medical establishments inflicted on minority communities, which has led to well-founded mistrust. But it is important to remember that hesitation is not the same as refusal, and the onus is on clinical investigators to invite participation and address fears up front.

Elderly patients or those who live in rural regions are also historically underrepresented in oncology trials, which tend to be run through academic medical centers. In many cases these institutions are located hundreds of miles from patients’ homes, and there’s evidence that this lack of access to clinical trials has an effect on patient outcomes. Data show that patients with cancer in rural communities tend to fare worse than their urban counterparts, but when trial participation was controlled for, the mortality gap between rural and urban patients vanished.

MEETING PATIENTS WHERE THEY ARE

Another part of the issue underlying clinical trial homogeneity is that enrollment in clinical trials is generally low. Despite the fact that oncology trials provide the opportunity to access the most advanced treatments not yet available in the clinic, less than 5% of patients with cancer in the US enroll in a clinical trial.

Instead, the vast majority are treated in community clinics. Designing trials that meet patients where they are could not only improve overall enrollment but also trial diversity, allowing for therapies to be tested on a population that is more representative of the patients we treat in our day-to-day practice. Otherwise, how are we to know that a treatment regimen tested mostly on young, White, urban individuals will work for patients who fit none of those characteristics?

This idea of bringing trials to the people is the heart of mission of the National Cancer Institute Community Oncology Research Program (NCORP)—a network of 46 community sites across the US, 14 of which are designated as minority/underserved sites that aim to make trials more inclusive to historically underrepresented groups (FIGURE).

Virginia Commonwealth University (VCU) Massey Cancer Center in Richmond is a Minority/Underserved NCORP (MU-NCORP) site and, as a principal investigator for the VCU MU-NCORP grant, I have seen firsthand how powerful this program can be when it comes to bringing high quality cancer care to individuals who need it most.

On average, approximately 30% of our clinical trial participants belong to racial and ethnic minority groups, which is much higher than the national average of 17%, thanks in no small part to the MU-NCORP program, which gets us out in the community—and not just when we are trying to recruit.
**BUILDING A COMMUNITY PRESENCE**

Since it is critically important to build a foundation of trust, first we cultivate a presence and open a dialogue in the community. We offer screening, prevention, and education programs, then, when the opportunity to participate in a trial arises, we are there to answer questions, dispel myths, and address fears.

For instance, many patients with cancer have the misconception that if they sign up for a trial, they may be given a placebo or they worry that the drug is experimental and untested. We tell patients that they will at worst receive the current standard of care and that most NCORP trials are phase 3, so the drugs have already been through rigorous phase 1 and 2 safety and efficacy testing in smaller groups before being deployed in large-scale community trials.

We also use social media platforms, such as Facebook Live, and attend health fairs and screening events to talk with individuals in the community about health. Through these events we also start conversations about obesity, smoking, and overall wellness—the foundations of cancer risk reduction.

Sadly, the COVID-19 pandemic put a damper on these efforts. Although Zoom may be accessible to some, it is less so for others, and we have had fewer participants overall. Losing these events in addition to a drop in in-person screening opportunities around the country may have contributed to cancer detection rates decreasing since March 2020. As we emerge from the pandemic, it will be critically important to get community cancer initiatives back on track.

**REFERENCES**

Persistent Development of WEE1 Pathway Inhibitors Begins to Pay Off

by JANE DE LARTIGUE, PhD

WEE1 IS A KEY REGULATOR of the cell cycle that has been a target of cancer drug discovery efforts for more than a decade. The lead novel candidate, the WEE1 inhibitor adavosertib (AZD1775), has been tested in more than 50 completed or ongoing clinical studies but has yet to proceed to a phase 3 trial despite showing promising safety and efficacy as monotherapy and in combination with a range of other cancer therapies.1,2

Now, however, adavosertib may have found its niche. Results from the first randomized phase 2 clinical trials in patients with ovarian cancer have emerged. Adavosertib in combination with chemotherapy demonstrated encouraging activity both in patients with platinum-resistant or -refractory high-grade serous ovarian cancer (HGSOC) and in those with platinum-sensitive TP53-mutant ovarian, fallopian tube, or primary peritoneal cancer compared with placebo plus chemotherapy.3,4

Findings from several other phase 2 clinical trials have demonstrated the potential of adavosertib in uterine serous carcinoma,5,6 pediatric neuroblastoma,7,8 and solid tumors amplified by CCNE1, the gene encoding cyclin E1.9 Positive results in CCNE1-amplified malignancies highlight the need for biomarkers to identify patients most likely to respond to WEE1 inhibition. Meanwhile, 2 novel highly selective WEE1 inhibitors, IMP7068 and Debio 0123, recently entered clinical testing and investigational therapies directed at kinases that regulate WEE1 activity have become promising drug targets (Table). Most notably, these targets include the ATR protein, a master regulator of the DNA damage response (DDR) pathway that acts to stabilize, protect, and coordinate replication forks.1,2 Numerous ATR inhibitors have entered clinical development, several of which recently demonstrated encouraging activity in patients with lung and ovarian cancers.1,10-12

AN ACHELLES HEEL

The DDR pathway, a network of hundreds of proteins that detect and respond to DNA damage, and the cell cycle are highly interconnected cellular processes, and many components of both are dysregulated in cancer cells to sustain their hallmark capacity for limitless cell division.13,14 Too much DNA damage is catastrophic, even for cancer cells, and requires a delicate balance in disabling enough DNA repair mechanisms to permit oncogenic alterations while avoiding triggering cell death. As a result, cancer cells can become heavily reliant on certain DNA repair pathways and cell cycle checkpoints, creating a potentially therapeutically tractable Achilles heel.1,14,15

WEE1, a kinase that serves as a molecular sentry at the G2-M checkpoint in the cell cycle, is one such target. In the presence of DNA damage, WEE1 blocks entry into mitosis by “switching off” the CDK1/cyclin B complex that would normally signal to the cell to proceed beyond this point.1,15,16

In normal cells, WEE1 acts as a tumor suppressor by preventing cells from passing on damaged DNA when they divide. The role of WEE1 in tumor cells is not fully understood and although reduced WEE1 expression has been observed in several tumor types, WEE1 also has been shown to be frequently overexpressed, which researchers have postulated is because tumor cells are dependent upon the G2-M checkpoint to maintain tolerable levels of genome instability.17

FIRST-IN-CLASS WEE1 INHIBITOR

Despite substantial interest in the idea of targeting WEE1, the development of WEE1 inhibitors to date has been essentially limited to adavosertib. Research began back in 2009, and since then, many clinical trials have evaluated adavosertib as both a single agent and in combination with chemotherapy and other drugs designed to induce DNA damage.1,15-17

The strategy for targeting WEE1 and DNA networks is based on a strong biological rationale and findings from preclinical studies suggesting that WEE1 inhibition has a synthetic lethal effect, whereby the combination of 2 defective genes is lethal to a cell but defects in either one alone is not. There was particular excitement surrounding the potential for WEE1 inhibition to target TP53-mutant cells, the most commonly mutated gene in cancer cells and one that remains stubbornly therapeutically intractable.18 However, the jury is still out on the correlation between TP53 status and clinical benefit from WEE1 inhibition.1,15

Adavosertib was well tolerated but showed limited efficacy as monotherapy, so the focus of clinical development shifted predominantly to combination therapy.1,17 In a number of advanced solid tumors, the combination of adavosertib and platinum-based chemotherapy and/or radiation therapy was shown to be effective.

Clinical development of adavosertib has progressed slowly, however, and data from randomized phase 2 clinical trials are just beginning to emerge. These results have reinvigorated enthusiasm for WEE1 inhibitors.

ADAVOSERTIB TRIAL FINDINGS

In a double-blind, randomized, placebo-controlled phase 2 trial (NCT02151292), 94 women with recurrent/platinum-resistant/refractory HGSOC received adavosertib (175 mg on days 1, 2, 8, 9, 15, and 16) in combination with gemcitabine (1000 mg/m² on days 1, 8, and 15) in 28-day cycles or placebo plus gemcitabine.3
WEE1 IS A PROTEIN KINASE that regulates the G2-M cell cycle checkpoint.1,2 The cell cycle is the series of steps that cells pass through prior to dividing to form new cells. Nondividing cells are found in the quiescent G0 phase and, in response to mitogenic stimulation, enter the first growth phase (G1), followed by DNA replication during S phase and a second growth phase (G2) before the cell undergoes mitotic (M) division.3,4

Progression from one stage to the next is tightly controlled by a swath of proteins that ensure each step occurs at the appropriate time. Among them are cyclin-dependent kinases (CDKs), which execute their cell cycle functions only when bound to cyclins, a group of proteins with levels that oscillate throughout the cell cycle.3,4

CDK/cyclin complexes control a series of checkpoints at which the cell cycle can be stopped if problems arise, such as damage to the DNA. Checkpoints occur at the G1-S transition, during S phase, between G2 and M, and during mitosis.3,4

The G2-M transition is regulated predominantly by the CDK1/cyclin B complex. Before mitosis, WEE1 keeps CDK1 in an inactive state by phosphorylating it at a key tyrosine residue (tyrosine 15). As the cell approaches the G2-M transition, in the absence of DNA damage, the levels of WEE1 begin to decline as it is phosphorylated by the PLK1 protein, which targets WEE1 for destruction by the ubiquitin-proteasome system. A second target of PLK1 is CDC25, a phosphatase that removes the inhibitory phosphate group on tyrosine 15 of CDK1, thereby activating it and triggering progression into mitosis (FIGURE 1).5,6

A coordinated network of signaling pathways, known as the DNA damage response (DDR), senses DNA damage and feeds into the cell cycle to trigger checkpoints and allow the cell time to repair the damage.7,8

The ATR kinase is a central regulator of the DDR.8 In response to DNA damage, ATR activates CHK1, another kinase that mainly targets CDC25 and WEE1. This leads to activation of WEE1 and degradation of CDC25, halting the cell cycle at the G2-M checkpoint.5,6

As a result of common defects in the G1-S checkpoint, cancer cells become more dependent upon a functional G2-M checkpoint to prevent catastrophic DNA damage that would trigger cell death. Thus, blocking the activity of kinases like WEE1 could disable this checkpoint and allow targeted killing of cancer cells.5,6

REFERENCES

FIGURE. WEE1’s Role in the Cell Cycle1
The addition of adavosertib to gemcitabine yielded a statistically significant improvement in median progression-free survival (PFS), the primary end point of the study, to 4.6 months (95% CI, 3.6-6.4) compared with 3.0 months (95% CI, 1.8-3.8) with placebo (HR, 0.55; 95% CI, 0.35-0.90; log rank \( P = .015 \)).

The secondary end point of median overall survival (OS) also showed an advantage with the combination. In the final analysis, median OS was 11.4 months (95% CI, 8.2-16.5 months) among patients treated with adavosertib plus gemcitabine and 7.2 months (95% CI, 5.2-13.2 months) among those in the placebo arm (HR, 0.56; \( P = .017 \)). There was also an improvement in the proportion of patients with intermittent dose modifications.3

The benefit of adavosertib came at the expense of increased toxicity, with more frequent grade 3/4 neutropenia (62% vs 30%), decreased white blood cell counts (54% vs 18%), and thrombocytopenia (31% vs 6%) in the adavosertib arm vs the placebo group, respectively, but there were no treatment-related deaths. Investigators said the hematologic effects were consistent with previous study findings and “generally manageable” with intermittent dose modifications.1

In a second randomized phase 2 trial (NCT01357161), patients with platinum-sensitive ovarian cancer with TP53 mutations were randomized to receive adavosertib (225 mg twice daily for days 1 and 2, and then on the morning of day 3) concomitantly with paclitaxel (175 mg/m²) and carboplatin (area under the curve of 5) on day 1 in 21-day cycles.5

<table>
<thead>
<tr>
<th>Drug (sponsor)</th>
<th>Tumor type(s)</th>
<th>Phase(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adavosertib (AZD1775) (AstraZeneca)</td>
<td>Uterine serous carcinoma; recurrent ovarian, primary peritoneal, or fallopian tube cancer; CRPC; GE advanced solid tumors with PARP resistance</td>
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<tr>
<td>IMP7068 (Impact Therapeutics)</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>Debio 0123 (Debiopharm)</td>
<td>Advanced solid tumors</td>
<td>1</td>
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### ATX inhibitors

<table>
<thead>
<tr>
<th>Drug (sponsor)</th>
<th>Tumor type(s)</th>
<th>Phase(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berzosertib (M6620) (EMD Serono)</td>
<td>Relapsed platinum-resistant SCLC; soft tissue sarcoma; DDR-deficient metastatic/unresectable solid tumors; advanced squamous cell NSCLC; locally advanced HNSCC; chemotherapy-resistant TNBC or HR+; HER2-advanced breast cancer; recurrent and metastatic ovarian, primary peritoneal, or fallopian tube cancer</td>
<td>1, 1/2, 2</td>
</tr>
<tr>
<td>Ceralasertib (AZD6738) (AstraZeneca)</td>
<td>Recurrent osteosarcoma; treatment-naive ES-SCLC; advanced HER2+ solid tumors; advanced solid tumors</td>
<td>1, 1/2, 2</td>
</tr>
<tr>
<td>M4344 (EMD Serono)</td>
<td>Advanced solid tumors/breast cancer; PARP inhibitor-resistant ovarian cancer</td>
<td>1/2, 1</td>
</tr>
<tr>
<td>Elimusertib (BAY-1895344) (Bay)</td>
<td>Advanced/metastatic cancers of the stomach and intestines; advanced solid tumors/ovarian cancer; recurrent HNSCC</td>
<td>1</td>
</tr>
<tr>
<td>RP-3500 (Repate Therapeutics Inc)</td>
<td>Advanced solid tumors</td>
<td>1/2</td>
</tr>
<tr>
<td>ART0380 (Artios Pharma Limited)</td>
<td>Advanced/metastatic solid tumors/ovarian cancer</td>
<td>1/2</td>
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</table>

### CHK1 inhibitor

<table>
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<tr>
<th>Drug (sponsor)</th>
<th>Tumor type(s)</th>
<th>Phase(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prexasertib (LY2606348) (St Jude Children’s Research Hospital)</td>
<td>Children/adolescents with relapsed/refractory group 3/group 4 or SHH medulloblastoma brain tumors</td>
<td>1</td>
</tr>
</tbody>
</table>

CRPC, castration-resistant prostate cancer; DDR, DNA damage response; ES-SCLC, extended-stage small cell lung cancer; GE, gastrointestinal junction; HNSCC, head and neck squamous cell carcinoma; HR, hormone receptor; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; SHH, sonic hedgehog, TNBC, triple-negative breast cancer.

*Trials are listed on ClinicalTrials.gov.

### TABLE. Select WEE1 Pathway Inhibitors in Clinical Development

### BEYOND OVARIAN CANCER

Adavosertib also has started to generate enthusiasm as a treatment for patients with uterine serous carcinoma, an aggressive and challenging form of endometrial cancer that has also been shown to display frequent dysregulation of cell cycle components.5,6 In a single-arm, 2-stage phase 2 study (NCT03668340), the results of which were published in the Journal of Clinical Oncology in March, 34 women who had undergone a median of 3 prior lines of therapy received adavosertib 300 mg once daily for the first 5 days and then on days 8 to 12 in 21-day cycles.5

With a median follow-up of 5.9 months, the ORR was 29.4% (95% CI, 15.1%-47.5%), with 1 confirmed complete response (CR), 8 confirmed PRs, and 1 unconfirmed PR, with a median DOR of 9.0 months (95% CI, 5.5-not available). Median PFS was 6.1 months (95% CI, 4.2-9.9 months).

Hematologic adverse effects (AEs) were common, including grade 3 and above anemia, neutropenia, and thrombocytopenia in 23.5%, 17.6%, and 32.4% of patients, respectively, and common nonhematologic AEs included diarrhea (76.5%), fatigue (64.7%), and nausea (61.8%). Biomarker analyses were performed, but no specific molecular alterations were found to be associated with clinical outcomes.3

Adavosertib in combination with irinotecan also recently showed promise in a
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cohort of patients with pediatric neuroblastoma enrolled in the phase 2 dose-expansion portion of an ongoing phase 1/2 clinical trial (ADVL1312; NCT02093132). During dose escalation, 27 evaluable patients received adavosertib in combination with irinotecan in 5 different dose cohorts on days 1 to 5 of 21-day cycles. Dose-limiting toxicities, which were observed at a dose of 110 mg adavosertib plus 90 mg/m²/day irinotecan, consisted of 2 patients with grade 3 dehydration and 1 each with diarrhea and hypotension. A patient with Ewing sarcoma had a confirmed PR with 1 and with ependymoma, had prolonged stable disease (SD) for 6 or more cycles. In the dose-expansion phase, patients in 3 pediatric disease-specific cohorts (neuroblastoma, medulloblastoma, and rhabdomyosarcoma) received the recommended phase 2 dose of 85 mg/m² of oral adavosertib plus 90 mg/m²/day of irinotecan for 5 days of every 21-day cycle.

Results presented at the American Association for Cancer Research Annual Meeting 2021 (AACR 2021) detailed 3 objective responses among 20 eligible patients with neuroblastoma, including 1 CR, 1 measurable PR, and 1 marrow-evaluable PR. Three patients also experienced prolonged SD of 8, 11, and 13 cycles. Investigators said only 1 patient had a dose-limiting toxicity, which was managed with a dose reduction.

Additionally, of 9 patients with predicted a deficiency of ATRX, a chromatin remodeler associated with poor outcomes in some neuroblastoma subtypes, 4 (44%) had objective responses or prolonged SD, suggesting a potential biomarker that warrants further investigation.

Meanwhile, a phase 2 trial in patients with CCNE1 amplification (NCT03253679) reinforced preclinical studies that suggested tumors with this molecular alteration are highly sensitive to WEE1 inhibition, according to findings presented at AACR 2021. Among 27 evaluable patients with 12 tumor types who had received a median of 4 prior lines of therapy over a median follow-up of 11.7 months, there were 7 confirmed PRs for an ORR of 25.9% (95% CI, 15.1%-47.5%), including 5 patients with HGSOC, and an additional 8 patients with HGSOC had SD for 6 months or longer.

Grade 3 and higher AEs included neutropenia, thrombocytopenia, anemia, nausea, diarrhea, and fatigue. Trial recruitment has been suspended pending a protocol amendment required for expansion, according to information posted on ClinicalTrials.gov.

Adavosertib targets 8 kinases, in addition to WEE1, albeit with lower potency, but there is still room to improve upon its selectivity. Two novel, more selective WEE1 kinase inhibitors have recently entered clinical development. Impact Therapeutics, based in China, is developing IMP7068 and was recently granted permission by the Chinese National Medical Products Administration to begin phase 1 trials. Debio 0123 was initially developed by Almac Discovery and subsequently licensed by Debiopharm, which has begun a first-in-human clinical trial of Debio 0123 in combination with carboplatin in patients with advanced solid tumors (NCT03968653).

**ATR AND CHK1 AS TARGETS**

In addition to WEE1 inhibitors, drugs targeting ATR and CHK1, which sit upstream of WEE1 in the DDR pathway, are also being developed. CHK1 inhibitors have struggled with tolerability and only prexasertib (LY2606368) is currently in clinical testing. Eli Lilly and Company reportedly dropped development of prexasertib in 2019 and the drug is not currently listed in the company’s oncology pipeline. However, several clinical trials are listed as active according to ClinicalTrials.gov, sponsored by various research institutions, with Eli Lilly and Company listed as a collaborator.

ATR inhibitors have proven much more promising, and multiple such drugs have rapidly entered clinical trials. The most widely studied are berzosertib (M6620) and ceralasertib (AZD6738). Berzosertib has been shown to be well tolerated in combination with different chemotherapy regimens in patients with advanced solid tumors.

Phase 2 data in patients with HGSOC and small cell lung cancer (SCLC) were recently reported. Among 25 patients with SCLC, berzosertib plus topotecan resulted in an ORR of 36%, including durable regressions in patients with platinum-resistant disease. A randomized phase 2 trial of this combination is currently ongoing (DDRiver SCLC 250; NCT04768296).

In a randomized phase 2 study of berzosertib plus gemcitabine compared with gemcitabine alone in patients with platinum-resistant HGSOC, the median PFS was 22.9 weeks (90% CI, 17.9-72 weeks) in the combination arm compared with 14.7 weeks (90% CI, 9.7-36.7 weeks) in the gemcitabine monotherapy arm (HR, 0.57; 90% CI, 0.33-0.98; P = .044).

In the ongoing phase 2, biomarker-directed HUDSON umbrella study (NCT03334617) in patients with non–small cell lung cancer, a combination of ceralasertib and the PD-L1 inhibitor durvalumab (Imfinzi) in patients with ATM mutations (n = 18) elicited an ORR of 13.3%, 6-month PFS of 61.2%, and 6-month OS of 100%.

For a full list of references, see the article at OncLive.com.
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by CHRISTINA T. LOGUIDICE

TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY (TA-TMA) is a complication of stem cell transplants that can occur with peripherally mobilized stem cells or bone marrow-derived stem cells. “TA-TMA remains a difficult complication to address, with a high mortality rate and a lack of standard diagnostic criteria and limited therapeutic options,” Samer Khaled, MD, said during a recent OncLive Peer Exchange®.

Khaled was joined by a panel of adult and pediatric hematology-oncology experts who provided an overview of TA-TMA, including findings that raise suspicion of this complication, strategies they use for making the diagnosis, and how they intervene given limited treatment options. They also discussed some off-label treatments and the emerging treatment narsoplimab (OMS721), a human monoclonal antibody that is under review by the FDA.

OVERVIEW OF TA-TMA
TA-TMA is triggered by injury to endothelial cells, such as from radiation, use of calcineurin or mTOR inhibitors, infections, or chemotherapy. However, this first hit to the endothelial cells is not considered sufficient to cause TMA. A second hit is needed, which the panelists explained is activation of the complement system, a part of the immune system made up of many distinct plasma proteins that react with one another in a cascade to destroy pathogens and fight infection. The same factors that damage endothelial cells also activate the complement system, the panelists noted.

“If injured endothelium exposes certain molecules, known as DAMPs [damage-associated molecular patterns], which bind a molecule known as MBL, mannan-binding lectin. MBL then activates MASP-2 [mannan-binding lectin-associated serine protease-2], which is an important enzyme in the cascade of a part of a complement system known as the lectin pathway. When activated, the lectin pathway itself can also then turn on the alternative pathway of complement. It is always on at very low levels waiting for a foreign invader or endothelial cell injury. Now you have marked activation of the lectin pathway and the complement pathway and the alternative pathway of complement in this system. If you can’t shut it off and it’s progressive, that can lead to 1 of these TA-TMAs,” Jeffrey Conrad Laurence, MD, explained.

The panelists said that there are some key differences with TA-TMA in pediatric vs adult patients. One distinction is that they are seen almost exclusively with allogeneic transplants in adults, whereas they occur with both autologous and allogeneic transplants in children. Only Khaled
reported seeing a few cases in adults undergoing autologous transplants. “At City of Hope we had a protocol for an autologous transplant for scleroderma, and I saw a couple of cases on that protocol,” he said, noting that he has also seen 1 or 2 cases over the last 12 years in patients who received autologous transplants for myeloma.

Another key distinction is that TA-TMA in pediatric patients appears to have a genetic component, whereas in adults no gene polymorphisms appear to contribute to the condition. “[In a study by Jodele et al1], upward of 30% to 40% of her pediatric patients who developed TMA had some recognized mutation in a complement coagulation or complement-regulatory factor gene. Whereas in our studies at Weill Cornell Medicine, we never found that. In many other series in adults, it’s incredibly rare to find those kinds of genetic mutations. There may be something special about that [pediatric] population with higher underlying inability to control complement that makes the incidence much greater,” Laurence said.

Determining the incidence of TA-TMAs is challenging because diagnostic criteria did not exist until relatively recently and those now available also vary somewhat. “In fact, it depends on whether you really want injury to happen and then make a diagnosis, or do you want early diagnosis. The more stringent the criteria you apply, the less the incidence will seem,” Parameswaran Hari, MD, MRCP, said. Nevertheless, based on his experience, he suspects the incidence in adult patients to be in the 10% range for TA-TMAs that are of clinical consequence following a first allogeneic transplant. He noted that the incidence increases with a second transplant, reaching 15% to 20%.

In pediatric patients, the panelists noted the incidence is higher than in adults, ranging between 20% and 30%. “When I think about the difference between the adult and pediatric populations and the incidence, one of the questions that comes to mind is: Is it a difference in the patients, is it a difference in the treatment, or is it a difference in the providers?” Christine N. Duncan, MD, said.

She explained it’s probably a combination of these factors, but that one of the main contributors is likely the screening criteria that were developed for children, which have helped raise awareness of the disease in the pediatric setting.

**DIAGNOSTIC CRITERIA FOR TA-TMA**

A variety of diagnostic criteria for TA-TMA now exist, including those by the LeukemiaNet International Working Group, Blood and Marrow Transplant Clinical Trials Network, and the Jodele criteria, among others.2,4 In pediatric patients, Duncan said “there is relatively uniform acceptance of the Jodele criteria” (TABLE 1). “We’re looking if you can meet 4 of the 7 criteria...but we don’t necessarily always say you have to meet all those points. If we have someone who has hypertension and proteinuria, we’re not going to wait and check everything else off to make sure they absolutely fulfill the criteria,” Duncan said.

The other available diagnostic criteria look at many of the same measures, with some also examining additional markers, such as the direct Coombs test, which should be negative in the setting of TA-TMA; coagulation studies, which should be normal; haptoglobin levels, which may be decreased; and creatinine levels, which may point to TA-TMA when elevated to twice the baseline level.2,3 The panelists proceeded to discuss the clinical and laboratory markers that they pay particular attention to. Hari said lactate dehydrogenase (LDH) level is a big marker at his institution, which implemented a policy to check patients’ LDH levels twice weekly while they are in the hospital following transplantation. He said this measure has helped them identify more TA-TMA cases. On the pediatric side, Duncan said they also test LDH levels in all patients once or twice weekly. “You don’t even have to think about it much if that is part of your routine on an inpatient, and if you see that with your lab values, that helps to trigger [a diagnosis],” she said. Duncan said another red flag in the pediatric setting is hypertension since this population rarely has it as a preexisting condition, though some degree of blood pressure elevation is expected from use of calcineurin inhibitors, steroids, and other agents.

Although ADAMTS13 activity is not part of any diagnostic criteria for TA-TMA, Laurence and Hari said they perform this test on all their transplant patients to help rule out thrombotic thrombocytopenic purpura (TTP). Making the distinction is important because patients with TTP can benefit from plasma exchange, whereas those with TA-TMA do not. “I noticed that in 3 large transplant studies the aggregate hematologic response to plasma exchange in a TA-TMA was 55%; that included a decrease or normalization of the LDH,

### TABLE. Laboratory and Clinical Markers Indicating TMA per Jodele Criteria

<table>
<thead>
<tr>
<th>Marker</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Elevated LDH</td>
<td>Increased above ULN for age</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Protein concentration ≥ 30 mg/dL on random urinalysis</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt; 18 years: BP at 95th percentile for age, sex, height; ≥ 18 years: BP ≥ 140/90 mm Hg</td>
</tr>
<tr>
<td>De novo thrombocytopenia</td>
<td>Platelet count &lt; 50 × 10^9/L or ≥50% decrease in platelet count</td>
</tr>
<tr>
<td>De novo anemia</td>
<td>Hemoglobin below the lower limit of normal for age or anemia requiring transfusion support</td>
</tr>
<tr>
<td>Evidence of microangiopathy</td>
<td>Schistocytes in the peripheral blood</td>
</tr>
<tr>
<td>Terminal complement activation</td>
<td>Elevated plasma concentration of sC5b-9 above upper normal laboratory limit</td>
</tr>
</tbody>
</table>

BP, blood pressure; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy; ULN, upper limit of normal.
increase in haptoglobin, and increase in platelet count. That 55% response rate to plasma exchange had no impact on mortality...the patients died with normal numbers,” Laurence said. He added that he no longer performs therapeutic plasma exchange for his TA-TMA patients.

TREATMENT APPROACHES FOR TA-TMA
One of the key treatment strategies for TA-TMA is to stop any offending agents, including any calcineurin or mTOR inhibitors. “We recommend substituting higher doses of steroids and CellCept [mycophenolate mofetil],” Laurence said. He explained another important measure is to look for and treat any underlying or coexisting conditions, such as infections, graft-vs-host disease (GVHD), or hypertension. The literature suggests these measures may be sufficient to resolve 50% to 60% of TA-TMA cases. The remainder require consideration of a variety of off-label or experimental agents, Laurence said, particularly agents that target the complement system, such as eculizumab (Soliris), defibrotide (Defitelio), or narsoplimab, since there are currently no approved treatments for TA-TMA and resolution of TA-TMA is imperative for improving overall survival (OS).

Eculizumab
Eculizumab is a monoclonal antibody that inhibits complement protein C5. It is approved by the FDA for the treatment of atypical hemolytic uremic syndrome (aHUS), another complement-mediated disease. “[In TA-TMA,] it’s probably more used in pediatric population than in the adult population,” Khaled said.

Thus far, eculizumab has been studied in a small clinical trial of 64 pediatric patients with high-risk TA-TMA and multiorgan injury. One year after hematopoietic stem cell transplantation (HSCT), the survival was 66% in the eculizumab-treated group. This was a significant improvement from the 16.7% survival rate observed in a previously reported untreated cohort that had the same high-risk TMA features. Patients with a higher sC5b-9 level at the start of eculizumab therapy were found to be less likely to respond to treatment and to require more drug doses.

“We use [eculizumab] quite frequently. If a patient has received a diagnosis of TA-TMA and has any degree of significance or injury to them, there’s always a conversation,” Duncan said. She noted that there are several key challenges with the use of eculizumab, including a lack of consensus on how long patients need to be treated, uncertainly regarding optimal dosing (eg, when to go up, how to space), and challenges receiving authorization for this drug in the outpatient setting. Additionally, its use requires prophylactic immunization and antibiotics against a variety of infectious organisms, including *Neisseria meningitidis* and *N gonorrhoea* in adults, as well as a variety of encapsulated organisms in pediatric patients.

Defibrotide
Defibrotide was approved by the FDA for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation in 2016, but Hari said this drug has been used for decades in Europe. While its precise mechanism of action remains unknown, he said “it’s an anti-inflammatory agent [that] can be thought of as an endothelial stabilizing agent.”

Defibrotide has shown some promise in treating TA-TMA. “There is definitely a subgroup of people who respond to it—not as promising as a dedicated mannose-binding lectin pathway inhibitor, perhaps, but I think that 1 hit of the endothelium might be able to be helped by this agent,” Hari said. However, a challenge is its bleeding risk, which is especially problematic in a patient population that is already at high risk of hemorrhage. Cost is another issue. “We don’t use too much of [it], unless we have some evidence of liver damage, because of the payment issues, at least in this country,” Hari said.

Narsoplimab
Narsoplimab is an inhibitor of MASP-2, which is the effector enzyme of the lectin pathway of the complement system. The FDA has granted this agent breakthrough therapy designation for high-risk HSCT-TMA and orphan drug designation for the prevention of complement-mediated TMAs and for the treatment of HSCT-TMA. The drug’s manufacturer, Omeros Corporation, has submitted a biologics license application to the FDA for narsoplimab as a treatment of HSCT-TMA, and the FDA has extended its review period, setting a new action date of October 17, 2021.

Narsoplimab has shown benefit in a small, single-arm, open-label pivotal trial that included 28 adult patients (median age, 48 years) with HSCT-TMA and high comorbidity burden. Protocol-specified treatment was IV narsoplimab 4 mg/kg or 370 mg once weekly for 4 or 8 weeks, with a 6-week follow-up period. The primary end point was complete response (CR) rate, which required improvement in 2 categories: laboratory markers of TMA (ie, LDH, platelet count) and organ function (ie, kidney, pulmonary, gastrointestinal [GI], neurological).

“The complete response rate was actually very appealing: It was 61% of all treated patients and 74% for the per-protocol set...Those are the patients who received 4 weeks or more on protocols,” Khaled said. Among both cohorts, 72% of patients showed substantial improvement in organ function, with greater than 65% showing improvements in kidney function, 50% showing improvements in neurological function, and 100% showing improvement in GI function.

When looking at the median OS, it was 274 days for all treated patients and 361 days for the per-protocol patients, with the median OS not reached in patients who had a CR. “This is really compelling data for this molecule, Khaled said. The other panelists agreed. “I think the availability of a pathophysiologically targeted agent addresses what really is at the bottom of the problem,” Hari said.

What makes the data even more compelling is that narsoplimab appears to have a highly favorable safety profile. Unlike eculizumab, it does not require the use of prophylactic immunization or antibiotics and it was found to be well-tolerated, even in a population with a high comorbidity burden. The most common adverse effects (AEs) included pyrexia, diarrhea, vomiting, nausea, neutropenia, fatigue, and
hypokalemia, all of which are common in the setting of HSCT. In total, 6 patients died during the core study period, with the causes of death being common in HSCT (eg, septic shock, GVHD, TMA).

LOOKING AHEAD
In addition to narsoplimab, several other agents are in late-stage development, including ravulizumab, a long-acting C5 inhibitor engineered from eculizumab. It is currently being studied in 2 phase 3 trials, including 1 in pediatric patients (NCT04557735) and 1 in adolescent (≥ 12 years) and adult patients (NCT04543591).14,15 Another promising agent is nomacopan (Coversin), a bifunctional inhibitor of C5 and leukotriene B4 that is being studied in a phase 3 trial in pediatric patients aged 6 months to 18 years who develop TMA within 100 days of HSCT, which is the period when most TMAAs requiring intervention occur.16

In his concluding remarks, Laurence encouraged health care providers to think about the pathophysiology of TA-TMA when caring for their HSCT patients. “Don’t just tread water doing things like plasma exchange or Rituxan [rituximab] unless there’s a specific indication for an autoantibody present. Think about trials of these newer experimental agents, which look very promising,” he said.

REFERENCES
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