Home Infusion Trend Stirs Debate

PEER EXCHANGE
Overcoming Toxicities Opens Door for BCMA in MULTIPLE MYELOMA

Not All BRCA Mutations Are Created Equal

ESMO CONGRESS 2021
Experts Review Practice-Changing Abstracts
Jared Weiss, MD, on IMpower010 Data in NSCLC
Daniel G. Stover, MD, Highlights DESTINY-Breast03 in HER2-positive BREAST CANCER
Jason Luke, MD, Discusses KEYNOTE-716 Applications in MELANOMA

CLINICAL PERSPECTIVES
Bradley J. Monk, MD, FACS, FACOG, Reviews Transformative Data in CERVICAL CANCER

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES WINTHROP P. ROCKEFELLER CANCER INSTITUTE
UAMS Winthrop P. Rockefeller Cancer Institute Pushes LIQUID BIOPSY Research Forward
By Donald J. Johann Jr, MD, MSC
FORGE AHEAD
WITH A BOLD APPROACH

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY
BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.
Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.
Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS.

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

Learn more at BLENREPHCP.com
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 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 the same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

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

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 1 in 13%. 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, 19% received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

Notable requirements of the BLENREP REMS include the following:

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

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

### 5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenia event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 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 premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

### 5.5 Embryo-Fetal Toxicity

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

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

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### 6 ADVERSE REACTIONS

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

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

#### 6.1 Clinical Trials Experience

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

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

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

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

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

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

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

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

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

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

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

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.
* Visual acuity changes were determined upon eye examination.
* Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
* Dry eyes included dry eye, ocular discomfort, and eye pruritus.
* Fatigue included fatigue and asthemia.
* Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthemia, hypertension, lethargy, tachycardia.

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.
8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

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

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

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS

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

• Patients must complete the enrollment form with their provider.

• Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia

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

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].

• Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.9), Use in Specific Populations (8.3)].

• Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

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

Infertility

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

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Strategic Alliance Partnership

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 62.
Home Infusion Trend Stirs Debate

by MEIR RINDE

As drug delivery systems continue to evolve, apprehensions over the shift toward in-home infusion care are intensifying. Despite innovations in chemotherapy treatments, safety concerns for at-home delivery of certain products as well as questions over cost present hurdles for providers and patients.

From the Physician’s Desk
16 Treatment Landscape Shifts Away From Chemotherapy Toward Targeted Approaches in ALL
By Matthew J. Wieduwilt, MD

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Drug Spotlight: Mobocertinib (Exkivity)
Changing the Course for Investigation and Care

**AS 2021 APPROACHES ITS CONCLUSION**, plans for the new year are starting to take shape. On the heels of the 2021 European Society for Clinical Oncology, leading experts reflected on the practice-changing data and how these may change the standard of care for certain patient populations in 2022 and beyond. In this issue of *OncologyLive®,* our editorial team spoke with several investigators to unpack the major trends and data that may influence practice for patients across tumor types.

A sentiment that ran through all responses was despite unprecedented progress, there is work be done. For example, data from the 3-year follow-up of the phase 3 CASPIAN trial (NCT03043872) showed that the addition of durvalumab (Imfinzi) to platinum-etoposide maintained a significant survival benefit in patients with extensive-stage small cell lung cancer vs platinum-etoposide alone. At the data cutoff 3 times more patients estimated to be alive when treated with the anti-PD-L1 chemotherapy combination, and investigators concluded that the regimen should be considered the first-line standard of care for this patient population (3-year overall survival rates were 17.6% vs 5.8%, respectively).1

“I want to emphasize the fact that trials, in particular immunotherapy trials, should be followed up long term,” Luis Paz-Ares, MD, PhD, said in an interview with *OncologyLive®*. “I understand that hazard ratio is very important, median survival is very important, and [these are end points] that lung cancer physicians are used to. But here we have a new dimension, which is the long-term benefit [and] the potential for cure.”

Novel anticancer drugs and combinations represent a fraction of the shifting landscape for delivering quality care. As the cover story of this issue of *OncologyLive®* elucidates, debate on the future of at-home infusions sparks questions about whether this has the potential to become the next frontier of care.

Data concerning the safety of at-home infusion is sparse and organizations including the American Society of Clinical Oncology (ASCO) and the Community Oncology Alliance have issued positions opposing the delivery of intravenous chemotherapy regimens outside of the clinical setting. “The vast majority of the literature examines home infusion in general, which is of limited utility given the toxicity and hazardous materials specific to chemotherapy,” the ASCO board of directors said in a position statement.2

As these approaches to care continue to be debated in the community, the hosts of *OncLive On Air®,* a weekly podcast from *OncLive®,* will continue to provide expert insights on the latest data, trends, and information practicing oncologists need to provide the best patient care. Subscribe today by visiting onclive.com/podcasts.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES


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OncLive On Air™ is a podcast from OncLive®, which provides oncology professionals with the resources and information they need to provide the best patient care. In both digital and print formats, OncLive® covers every angle of oncology practice, from new technology to treatment advances to important regulatory decisions.

TUNE IN!
In our exclusive interview, Kathleen Moore, MD, provides perspectives on the ongoing research with the combination of VS-6766 and defactinib in ovarian cancer and the potential role for the treatment in clinical practice.

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Beyond the Peer-review Publication: Addressing Implications of Research for Patients

by MAURIE MARKMAN, MD

THE COIN OF THE REALM in the academic sector of oncology is the peer-reviewed publication. Authors understandably favor that their efforts be published in medical and oncology journals with the strongest objectively measured profiles, which are determined by proprietary algorithms created by various organizations.

Unfortunately, what is quantified in terms of the impact of a journal or individual article is the number of citations generated over a specified period in other peer-reviewed publications. In the opinion of this commentator, the actual focus of these efforts is to acknowledge the influence of the article or journal on other authors and investigators, rather than on the patients who may be the topic of the publication.

A related and concerning issue with regard to individual journal articles is what happens after the manuscript is published. Does the article do more than simply become a component of the résumé of the paper’s several authors, never to be seriously discussed again, or do the reported results serve as a stimulus for future investigation? Of course, industry would have a proprietary interest in published follow-up results of investigative efforts they commissioned or run, but what about publications that do not have an external sponsor willing or able to use the published results to directly affect patient care?

A provocative commentary by Naomi Oreskes in Scientific American discussed the question of the nature of science. “Science is a process of learning and discovery, and sometimes we learn that what we thought was right is wrong,” Oreskes wrote.

To explore the concept being highlighted in this commentary, I have selected 5 articles from a single issue of the journal Gynecologic Oncology (volume 162; July 2021), with the intention to review the potential implications for future research in the treatment of patients with gynecologic malignancies.

Investigators of the first article retrospectively examined 562 patients who underwent neoadjuvant chemotherapy at The University of Texas MD Anderson Cancer Center in Houston for advanced-stage ovarian cancer and identified factors that might predict success in subsequent interval cytoreductive surgery. Two factors were highlighted: presence of a germline BRCA mutation and administration of dose-dense paclitaxel chemotherapy, both of which were predictive of improved opportunities for successful surgery and progression-free survival. The question to be asked in this commentary is what effect will these results have on future treatment plans of these investigators and others viewing the findings? Will the results change practice, lead to further research efforts including attempting to obtain confirmatory data from other large treatment datasets, or simply be forgotten/ignored?

The second paper reported the risk of platinum-associated hypersensitivity reactions among 409 patient with ovarian cancer, 95 (23%) of whom had a BRCA mutation. The investigators found a doubling (9% to 18%) in the risk of an allergic reaction among the patients with a BRCA mutation. The question to be asked here is what are the clinical or future research implications of this observation? Should patients with BRCA mutations be more carefully observed for such events, perhaps counseled regarding the risk, or should additional investigation be undertaken by other centers to confirm or refute these findings?

Investigators of the third paper retrospectively examined an institutional experience with the efficacy and toxicity of pembrolizumab (Keytruda) plus lenvatinib (Lenvima) for the treatment of recurrent endometrial cancer. Among 70 patients, the investigators found that a reduced starting dose of lenvatinib was associated with less-serious adverse effects and no difference in response rates. The authors noted that “a lower starting dose of lenvatinib (14 mg daily) in combination with...
pembrolizumab was safe and efficacious in recurrent endometrial cancer” but appropriately added that “larger studies are required to validate these findings.” Is that study going to be initiated, and how will investigators work to ensure that appropriate randomized, controlled trials are conducted to confirm or refute this potentially highly clinically relevant observation?

A fourth study examined the National Cancer Database for the effect of fragmentation of care—surgery and chemotherapy delivered at different institutions—for patients who receive a diagnosis of ovarian cancer. In a population of 36,300 patients, of whom 13,347 (36.8%) received such care, investigators found that fragmentation of care between primary surgery and subsequent chemotherapy did not have an adverse effect on long-term survival. How will these data be employed by an individual clinician when determining management options for an individual patient? For example, would they consider arranging for surgery to be undertaken in a high-volume center with multiple cycles of systemic treatment given nearer to the patient’s home?

Finally, investigators of a highly provocative study examined the effect of a substantial decrease in the use of minimally invasive hysterectomy for the treatment of cervical cancer in the United States. Investigators found that following the publication of landmark data that reported the risk associated with the minimally invasive approach, patients were 63% less likely to receive this surgical strategy. However, the retrospective analysis revealed the decreased use of minimally invasive surgery was associated with a greater risk of perioperative complications (23%). Therefore, the question to be asked here is how will this information be incorporated into future clinical trials in this arena or in the management of individual patients?

The information that appears in medical/scientific journals may add an important new component that can advance solutions to problems affecting patients, or it may be an observation of little relevance to anyone. But if the paper does not encourage further discussion and debate, challenge existing ideas or dogma, or provide support for current biological concepts or in the clinical realm for treatment of patients, what was its purpose?

REFERENCES
Brexxucabtagene Autoleucel Moves Forward for Relapsed or Refractory B-ALL

The FDA has granted approval to brexxucabtagene autoleucel (Tecartus) for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B-ALL). Support of the chimeric antigen receptor T-cell therapy is based on efficacy data from the phase 1/2 ZUMA-3 trial (NCT02614066). Among the 54 evaluable patients, the overall complete remission rate, which comprises complete remission (CR) with incomplete blood count recovery and CR, was 64.8% (95% CI, 51%-77%). The CR rate was 51.9% (95% CI, 37.8%-65.7%). With a median follow-up of 7.1 months, the median duration of CR was not reached (95% CI, 9.6-not estimable).

The product label includes a box warning for cytokine release syndrome and recommends withholding treatment from patients with active infection or inflammatory disorders and to treat life-threatening reactions with tocilizumab (Actemra) or tocilizumab and corticosteroids. There is an additional box warning for neurologic toxicities that recommends monitoring after treatment and providing supported care and/or corticosteroids as needed.

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

Cetuximab Plus Encorafenib Gets Go-Ahead for BRAF V600E–Mutant Metastatic CRC

The FDA has granted approval to cetuximab (Erbitux) plus encorafenib (Braftovi) for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

The new indication is supported by findings from the phase 3 BEACON CRC trial (NCT02928224). The median overall survival was 8.4 months (95% CI, 7.5-11.0) for the 220 patients who received the doublet compared with 5.4 months (95% CI, 4.8-6.6) for the 221 patients who received irinotecan plus cetuximab or leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI) with cetuximab (HR, 0.60; 95% CI, 0.45-0.79; P = .0003).

Per blinded independent central review, the median progression-free survival was 4.2 months (95% CI, 3.7-5.4) in the investigative arm vs 1.5 months (95% CI, 1.4-1.7) in the control arm (HR, 0.40; 95% CI, 0.31-0.52; P < .0001).

The combination elicited an overall response rate (ORR) of 20% (95% CI, 13%-29%), which included a 5% complete response rate and a 15% partial response rate with a median duration of response of 6.1 months (95% CI, 4.1-8.3). In the control arm, the ORR was 2% (95% CI, 0%-7%) and all responses were partial responses. The median duration of response was not reached (95% CI, 2.6-not reached).

TO READ MORE, VISIT bit.ly/3F4Ut6s.

Select Allogeneic CAR T-Cell Therapy Trials Paused After Report of Chromosomal Abnormality

The FDA has placed a hold on clinic trials examining Allogene Therapeutics Inc’s allogeneic chimeric antigen receptor (CAR) T-cell therapies for patients with cancer. The regulatory decision followed a report of a patient who experienced a chromosomal abnormality in ALLO-501A CAR T cells after treatment in the phase 1/2 ALPHA2-trial (NCT04416984).

Grade 1 cytokine release syndrome and grade 2 immune effector cell–associated neurotoxicity syndrome was observed, and the patient was given high-dose steroid therapy to treat these effects. The patient went on to develop progressive pancytopenia. Upon bone marrow biopsy, the patient demonstrated aplastic anemia and the presence of ALL-501A CAR T cells with a chromosomal abnormality.

The patient had achieved partial response to the CAR T-cell product and underwent allogeneic stem cell transplantation. Efforts are being made to further characterize the abnormality for better understanding on clinical relevance, evidence of clonal expansion, or its potential relationship to gene editing.

TO READ MORE, VISIT bit.ly/3iW35jT.

MSK Database Approval Opens Door for Potential Biomarkers

The FDA has granted recognition to a partial listing of Memorial Sloan Kettering (MSK) Cancer Center’s Oncology Knowledge Base (OncoKB) as the first tumor mutation database to be included in the Public Human Genetic Variant Databases.

The genetic variant database publicly documents evidence supporting links between human genetic variants diseases according to data submitted by researchers. The database provides developers of next-generation test developers with variant information to support the clinical validity of the tests.

On October 7, 2021, the FDA concluded that a subset of the OncoKB data and assertions are sorted into one of 2 levels of clinical significance consistent with FDA-authorized tumor profiling tests. Specifically, 46 genes were considered level 2 (cancer mutations with evidence of clinical significance) and 36 genes were considered level 3 (cancer mutations with potential clinical significance).

In total, OncoKB has detailed information regarding alterations in 682 cancer genes based on information curated from government agencies, professional groups, medical and scientific literature, and clinical trials. Investigators at MSK note that the primary audience for the full database is clinical oncologists and molecular pathologists.

TO READ MORE, VISIT bit.ly/2YNbmQf.
U.S. News & World Report has recognized Hackensack Meridian John Theurer Cancer Center at Hackensack University Medical Center as the best cancer center in all of New Jersey. And as a member of one of just 16 NCI-designated cancer consortia, we have distinguished ourselves as New Jersey’s premier cancer center—offering nationally recognized cancer specialists, clinical trials and immunotherapy including CAR T-Cell.

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
MOBOCERTINIB (EXKIVITY), a first-in-class oral EGFR tyrosine kinase inhibitor (TKI), has been granted accelerated approval by the FDA, establishing a new treatment option for patients with metastatic non–small cell lung cancer (NSCLC) that harbors \textit{EGFR} exon 20 insertion mutations. Specifically, this indication applies to patients whose disease has progressed on or after platinum-based chemotherapy.

The decision was based on efficacy and safety data from blinded independent central review of a phase 1/2 trial (NCT02716116), in which the agent elicited an overall response rate of 28% (95% CI, 20%-37%) among the 114 evaluable patients with 59% of responders having observed responses lasting longer than 6 months. The median duration of response (DOR) was 17.5 months (95% CI, 7.4-20.3).

In an interview with \textit{OncologyLive}®, Joel Neal, MD, PhD, associate professor in the Division of Oncology at the Stanford Cancer Institute at Stanford University in Palo Alto, California, discussed the evolving treatment landscape for patients with \textit{EGFR} exon 20–mutant NSCLC.

**What makes mobocertinib a novelty in this patient setting?**

Mobocertinib is a small-molecule EGFR TKI. It’s different than the available 5 EGFR TKIs because it has particular activity against the \textit{EGFR} exon 20 insertion mutation, which other \textit{EGFR} inhibitors inhibit minimally or not at all. Patients with \textit{EGFR} exon 20 insertion–mutant NSCLC had an unmet need for treatment directed against this mutation. Because the earlier EGFR TKIs didn’t inhibit this [mutation], patients could have a minor response lasting only a couple of months.

This drug provides a better response rate: 28% to 35% by independent and investigator review [respectively]. We also [looked at the] progression-free survival. [The median was] 7.3 months. It appears on the shorter side, probably because [approximately] two-thirds of the patients didn’t have a response or maybe didn’t have [central nervous system] control. But out of those [who did respond], those responses were remarkably durable [with a median DOR of] 17.5 months. Those data led to the approval of this agent, which is unique for this patient group with an unmet need.

**What adverse effects (AEs) do clinicians need to be aware of when prescribing mobocertinib?**

Predominantly diarrhea, which is manageable with anti-diarrheal medicines for most patients and occasionally by dose reduction. But I discourage [dose reduction] because the higher dose is better if the AEs can be managed. In addition, [other AEs associated with] \textit{EGFR} inhibitors may occur, including rash, rash with acniform, or dry skin on the face, chest, and back. There may be nausea, vomiting, and other \textit{[gastrointestinal]} AEs.

There are a few rare but serious AEs as well. These includes pneumonitis, as well as [heart rate–corrected QT] QTc prolongation, which rarely leads to problems such as Torsades de pointes. Keep an eye on interactions with other QTc-prolonging medications. I recommend frequent electrocardiograms for patients, especially when starting.

**How will the approval of both amivantamab (Rybrevant) and mobocertinib change the treatment paradigm for this patient population?**

I suspect that these drugs are going to be complementary, that the mechanism of action doesn’t preclude 1 from working after the other. Both represent novel ways to target \textit{EGFR} exon 20 insertion mutations. We could envision future clinical trials combining these strategies together to have better efficacy but also potentially more AEs.

I don’t think [investigators] are completely sure exactly how amivantamab is working so well [for those with] \textit{EGFR} exon 20 insertion mutations, whereas for \textit{EGFR} TKIs, we understand their ATP-competitive binding fairly well from other analyses. Amivantamab is unique, and I think that these are going to be complementary approaches.

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

The response rate of chemotherapy in the general [population of patients with] \textit{EGFR}-mutant lung cancer is approximately 20% [to] 50%. Progression-free survival may be 6 [to] 7 months, which is similar to what we saw for mobocertinib. This doesn’t mean that mobocertinib is ineffective, but the bar may be higher: to beat first-line chemotherapy. As a result, we’re considering possibilities such as combining mobocertinib with chemotherapy, which gives that additive effect together with chemotherapy.

[Investigators in] our field will move in the direction of considering combinations of these small molecule EGFR TKIs, such as mobocertinib, together with platinum chemotherapy. But for each individual patient, it’s great to have both options because the AEs are higher when we’re combining 2 different types of therapy together.

This [approval] represents a tremendous step forward based on research and rationally designed drugs for this group of patients with an unmet need. As we move forward with the combinations with chemotherapy and between different agents, [we must ask] how we better [develop] these drugs to [permeate] the brain. These patients are at high risk of central nervous system metastasis, and neither amivantamab nor mobocertinib nor chemotherapy has ideal central nervous system penetration.

**REFERENCE**

FDA approval—September 15, 2021
The FDA grants accelerated approval to mobocertinib (Exkivity) for the treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

**Mechanism of action:**
- Mobocertinib is an orally active, first-in-class, irreversible EGFR tyrosine kinase inhibitor that irreversibly binds to and inhibits EGFR via a covalent modification of Cys797 in the ATP binding pocket.

**How supplied:**
- 40-mg capsules

**Dose:**
- 160 mg orally once daily until disease progression or unacceptable toxicity

**Company:** Takeda Pharmaceuticals Inc

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**PIVOTAL CLINICAL TRIAL**
AP32788-15-101 (NCT02716116) was an international, nonrandomized, open-label, multicohort trial evaluating mobocertinib in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy.

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**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median age, years (range)</th>
<th>Median number of prior lines of therapy (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 (27-84)</td>
<td>2 (1-7)</td>
</tr>
</tbody>
</table>

**Number of prior lines of therapy**

- 41% 1
- 32% 2
- 27% ≥3

**Type of prior therapies**

- 43% Immunotherapy
- 57% EGFR TKIs
- 25% Brain metastases at baseline

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**EFFICACY IN THE AP32788-15-101 STUDY**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mobocertinib (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td></td>
</tr>
<tr>
<td>BICR (95% CI)*</td>
<td>28% (20%-37%)a</td>
</tr>
<tr>
<td>Investigator assessed (95% CI)</td>
<td>35% (26%-45%)</td>
</tr>
<tr>
<td>DOR</td>
<td></td>
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<tr>
<td>BICR</td>
<td>Median, months (95% CI)</td>
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<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>59%</td>
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<tr>
<td>Investigator assessed</td>
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<tr>
<td>Median, months (95% CI)</td>
<td>11.2 (5.6-NE)</td>
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<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>63%</td>
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</table>

BICR, blind independent central review; DOR, duration of response; NE, not estimable; ORR, overall response rate.

*Data for approval.

**RECOMMENDED MOBOCERTINIB DOSE REDUCTIONS FOR ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Dose reductions</th>
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<tr>
<td>First dose reduction</td>
<td>120 mg once daily</td>
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<tr>
<td>Second dose reduction</td>
<td>80 mg once daily</td>
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**COMMONLY REPORTED ADVERSE EFFECTS IN THE AP32788-15-101 STUDY**

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<tr>
<th>Adverse effect</th>
<th>Mobocertinib (n = 114)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
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<tr>
<td>Diarrhea</td>
<td>92%</td>
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<tr>
<td>Rash</td>
<td>78%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>46%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39%</td>
</tr>
</tbody>
</table>

* Events of grade 3/4

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**REFERENCES**

Treatment Landscape Shifts Away From Chemotherapy Toward Targeted Approaches in ALL

by MATTHEW J. WIEDUWILT, MD, PhD

TRADITIONAL CYTOTOXIC CHEMOTHERAPY-CONTAINING regimens have been the backbone of treatment for adults with acute lymphoblastic leukemia (ALL) for decades. Common complications of traditional chemotherapy can be fatal and include infection, bleeding, thrombosis, neuropathy, osteonecrosis, and the development of secondary cancers including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Compared with children with ALL, response and cure rates are substantially lower in adults. For patients over 60 years of age, traditional cytotoxic chemotherapy yields low cure rates, high treatment-related death rates, and poor long-term survival of less than 20%. For older adults, there has been minimal improvement in survival over the past 40 years despite marked improvement for adults under 60 years, adolescents, and children. For older patients, traditional chemotherapy approaches have largely failed.

Because the balance between efficacy and toxicity of chemotherapy has been reached for most adults with ALL, novel approaches with highly active, minimally toxic agents are needed to improve on traditional chemotherapy and possibly eliminate chemotherapy altogether. Tyrosine kinase inhibitors (TKIs) for Philadelphia-chromosome positive (Ph+) ALL, the anti-CD22-calicheamicin antibody-drug conjugate inotuzumab ozogamicin (Besponsa) for relapsed/refractory (R/R) B-cell ALL, and the anti-CD3/CD19 bifunctional T-cell engaging antibody blinatumomab (Blincyto) for R/R B-cell ALL have transformed care. Inotuzumab ozogamicin and blinatumomab are both superior for remission rates and survival compared with traditional chemotherapy in phase 3 studies in R/R B-cell ALL. Inotuzumab ozogamicin yielded high complete response rates (81%) and minimal residual disease (MRD)-negativity rates (78%) but with short median duration of remission (DOR; 4.6 months). Blinatumomab had a lower complete response (CR) rate than inotuzumab ozogamicin (44%) but a longer median DOR (7.3 months) and was found most effective in patients with low-burden disease in the marrow (lymphoblasts < 50%, CR rate 66%), suggesting that blinatumomab may be a highly effective agent in consolidation of remission in the frontline.

WHY AVOID TRADITIONAL SYSTEMIC CHEMOTHERAPY?

There are multiple answers that are appropriate: Traditional chemotherapy alone (1) is ineffective in most patients with certain types of ALL (such as Ph+ ALL); (2) has a high treatment-related mortality with low cure rates in older patients; (3) requires extended, complicated, and toxic treatment for 3 to 4 years; (4) is often only a bridge to allogeneic hematopoietic cell transplantation (HCT), which has a high rate of treatment-related morbidity and mortality; and (5) has long-term morbidity independent of allogeneic HCT including osteonecrosis of the bone, neuropathy, neurocognitive changes, and secondary cancers. Novel targeted agents are more active than traditional chemotherapy in ALL and maximizing their use in the front line may yield similar or superior results, even when combined with reduced-dose or no chemotherapy. Adding new agents to traditional chemotherapy also may lead to inferior outcomes as targeted agent doses are frequently reduced for toxicity when given in combination with chemotherapy and the combinations can have high non-relapse mortality that may erase any benefit of increased efficacy from adding the novel agent.

“Given the high activity of BCR-ABL1–targeted TKIs...approaches to reduce treatment-related mortality have been studied by reducing or eliminating chemotherapy.”
tyrosine kinase activity and is the genetic hallmark of chronic myeloid leukemia (CML) and Ph+ ALL. Historically a poor-risk disease, adults with Ph+ ALL had long-term survival rates of less than 20% with chemotherapy alone.5-7

TYROSINE KINASE INHIBITORS

The development and application of BCR-ABL1–targeted tyrosine kinases inhibitors (TKIs), such as imatinib mesylate (Gleevec), dasatinib (Sprycel), and ponatinib (Iclusig) in CML and Ph+ ALL has dramatically changed care and improved survival. An earlier study of imatinib with chemotherapy improved survival, principally by facilitating more patients proceeding to allogeneic HCT.7 Without allogeneic HCT most patients treated with imatinib relapsed due in large part to numerous different mutations in the BCR-ABL1 kinase domain (KD). Although encouraging benefits have been observed, resistance remains a challenge that is associated with TKI use.

Second-generation TKIs, such as dasatinib, overcome most TKI resistance by BCR-ABL1 KD mutation although they are ineffect against the T315I mutation seen in 70% to 75% of relapses in dasatinib-treated patients.8-10 The combination of second-generation TKIs with intensive chemotherapy appears to lead to superior outcomes to imatinib-based approaches. Investigators of SWOG 0805 (NCT00792948) evaluated dasatinib with hyper cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) in adults 60 years and younger with Ph+ ALL. Patients undergoing allogeneic HCT after dasatinib/hyper-CVAD induction had better survival than those receiving dasatinib and chemotherapy alone, supporting the use of allogeneic HCT in this population.11

Ponatinib, a TKI that overcomes resistance by most BCR-ABL1 KD mutations including T315I, has been studied in combination with hyper-CVAD. The combination was highly active with a CR rate of 100%, complete molecular response (CMR) rate of 78%, and 3-year event-free survival (EFS) of 70%.12,13

REDUCING OR ELIMINATING CHEMOTHERAPY

The toxicities of these intensive approaches are typically prohibitive for use in older adults with Ph+ ALL, the population with the highest incidence of the disease. Given the high activity of BCR-ABL1-targeted TKIs in Ph+ ALL, approaches to reduce treatment-related mortality have been studied by reducing or eliminating chemotherapy. GRAAPH-2005 (NCT00327678) randomized patients to imatinib with hyper-CVAD or with minimal chemotherapy. The CR rate was higher with the minimal chemotherapy approach (98% vs 91%, P = .006) principally because of increase induction death with hyper-CVAD.14 Studies of chemotherapy-free induction with TKIs with corticosteroids showed that the approach yields CR rates of 95% to 100% with minimal or no induction death.

Investigators of the GIMEMA study LAL1205 (NCT00391989) evaluated dasatinib with prednisone followed by provider choice of post remission therapy. The regimen was well tolerated with a CR rate of 93%. Relapse occurred in 74%, 36%, 11% of patients receiving post-remission therapy with TKI only, TKI with chemotherapy, and allogeneic HCT, respectively.4 A subsequent GIMEMA study, the D-ALBA study (NCT02744768), evaluated dasatinib and blinatumomab for 5 cycles, then dasatinib maintenance as post remission therapy after dasatinib/corticosteroid induction. The CR rate was 98% with excellent 18-month overall survival (OS) and disease-free survival (DFS) of 95% and 88%, respectively.15 At last report with 27 months follow-up, there were 9 relapses among 63 patients (4 systemic, 4 CNS, 1 nodal).16 Confirmatory data are awaited from the ongoing US Intergroup SWOG 1318 study (NCT02143414), which has completed accrual.

The failing of dasatinib because of BCR-ABL1 T315I ALL is being addressed by treating older patients with ponatinib and corticosteroids alone. An early report showed a high CR rate (95%) and favorable molecular response rate (CMR rate 46%) with short follow-up.17 More recently, investigators at the University of Texas MD Anderson Cancer Center in Houston reported early outcomes of ponatinib with blinatumomab. In newly diagnosed patients, the CR rate was 100%, CMR rate was 87%, and estimated 1-year OS and DFS rates were both 100%.18 Although extremely promising, long-term follow up is needed for durability of responses and late toxicity.
PH-NEGATIVE ALL

The road to chemotherapy-free regimens in Ph-negative ALL is just being paved given the recent availability of highly effective targeted therapies. For Ph-negative ALL, inotuzumab ozogamicin and blinatumomab are being actively studied as part of traditional chemotherapy regimens in randomized studies in the front line (eg, A041501, NCT03150693; EA1910, NCT02003222). Given the impressive activity of these agents in R/R ALL, studies are also evaluating them in chemotherapy-free induction or as chemotherapy-free regimens.

SWOG 1318 evaluated blinatumomab as induction therapy followed by 6-mercaptopurine, vincristine, methotrexate, prednisone maintenance for older, transplant-ineligible patients. The regimen was very well tolerated with a CR rate of 66%, MRD negativity rate of 92%, and a 1-year DFS rate of 56%. Inotuzumab ozogamicin has demonstrated a 100% CR rate and MRD negativity rate of 74% as induction in German Multicenter Study Group on Adult Acute Lymphoblastic Leukemia INITIAL-1 trial (NCT03460522) (TABLE). Given the success of higher dose of blinatumomab observed in those with low burden disease, investigators of Alliance A041703 (NCT03739814) are studying induction with 2 cycles inotuzumab ozogamicin followed by consolidation with 4 to 5 cycles of blinatumomab in older patients with results expected in 2022.

Advancements in chemotherapy-free regimens are improving outcomes in Ph-positive ALL and hold promise in Ph-negative ALL. Clinical trials have been and remain essential to continuing the transformative progress that has occurred in adult ALL in the past 5 years. Because of the novelty of these approaches and short follow-up on existing studies, questions will need to be answered including the optimal CNS prophylaxis, need for and/or duration of maintenance, antigen levels conferring benefit, the benefit of adding novel agents including BH3 mimetics such as venetoclax (Venclexta) or navitoclax, antibodies such as daratumumab (Darzalex), and checkpoint inhibitors, and mechanisms of resistance to inform future development of these therapies. It is hoped “chemo-free” approaches will set a new standard of care and form a backbone on which to build even more effective, highly tolerable, and convenient therapies with very high cure rates.

**REFERENCES**

THE COVID-19 PANDEMIC SPURRED the launching or expansion of in-home cancer therapy infusion programs at several oncology centers around the United States, drawing a surge of interest throughout the field as well as opposition from oncologists who are concerned about the implications for patient safety and the potential impact on community practices that provide in-house infusion services.

In addition to addressing COVID-19-related safety concerns, the potential cost savings from moving the site of care to patients’ homes has stoked interest from payers and specialty pharmacy companies. But Nathan R. Handley, MD, MBA, a medical oncologist at Sidney Kimmel Cancer Center — Jefferson Health in Philadelphia, Pennsylvania, said the primary driver for his center’s in-home infusion program is patient convenience.

“The goal is really to develop a cancer care delivery system that is more responsive to an individual patient’s needs,” Handley said. He helps run Jefferson’s in-home chemotherapy initiative, which was started in 2019.

“Coming into the infusion center can be very burdensome, especially if someone is coming to our downtown campus. If it’s an hour infusion, it’s not an hour of time; it’s like half a day. They have to get ready, they drive in, they park, they get bloodwork, and then they wait, and wait, and wait, and get their infusion.

“If they can minimally disrupt their life, that creates opportunities to have time with family, more time with work, more time to focus on priorities other than the physical act of getting their chemotherapy. Our goal is not for this to be something that everyone gets, but something we can have a conversation about with lots of patients.”

Although the concept of in-home infusion therapy is gaining adherents, the American Society of Clinical Oncology (ASCO) has expressed reservations about the safety of routinely administering anticancer drugs in patients’ homes and the Community Oncology Alliance (COA) has declared its staunch opposition. Neither group opposes portable therapy delivery through implantable infusion devices.1,2

When COVID-19 started to disrupt medical care in the spring of 2020, COA issued a statement saying the organization “fundamentally opposes home infusion of chemotherapy, cancer immunotherapy, and cancer treatment supportive drugs because of serious patient safety concerns.”2

As drug delivery systems continue to evolve, the debate over in-home infusion is likely to intensify. Industry analysts anticipate steady expansion in North American markets for home infusion therapies, with chemotherapy being one of the strongest drivers of growth.3,4

Additionally, an increase in FDA approvals for monoclonal antibodies administered via subcutaneous vs intravenous infusion, including several for treating patients with cancer, may contribute to demand for home-based care.5,6 In June 2020, the FDA approved PheSgo, a subcutaneous formulation that incorporates pertuzumab (Perjeta) and trastuzumab (Herceptin) with hyaluronidase–zzxf for the treatment of patients with HER2-positive breast cancer in combination with chemotherapy.7 The agency stated that “a qualified health care professional” can
administer Phesgo in the patient’s home once the chemotherapy portion of the treatment is completed.8

**CHANGING CHEMOTHERAPY LANDSCAPE**

Home infusion of cancer therapy is not a new idea. Take-home chemotherapy has been available for decades, principally in the form of ambulatory pumps infusing 5-fluorouracil (5-FU).9,10 To receive ambulatory therapy with 5-FU, patients are connected to the pump at a clinic, carry it with them for 48 hours, and return to the center to be disconnected or to receive a new pump. Handley said some centers also have been providing home infusion of high-dose cytarabine (HiDAC) or the 5-drug combination EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) for patients with hematologic malignancies.

Although portable infusion devices have become established in oncology care, home infusion of therapies represent another step. Starting in the 1980s, infusion therapy has shifted from hospitals to physician-owned or hospital-affiliated outpatient centers.2 Some experts regard in-home infusions as an innovation in the development of chemotherapy (FIGURE).9

Globally, an estimated 5% to 10% of patients with cancer receive oncology treatments at home.11 However, the practice of in-home infusional therapy has not been widely adopted in the United States.

That is starting to change. In 2019, both Jefferson and the University of Pennsylvania/Penn Medicine, also in Philadelphia, launched pilot programs that send nurses to the homes of patients with cancer to administer leuprolide (Lupron) injections or set up infusions of a number of different drugs. Those efforts accelerated in 2020 as the medical centers sought to keep patients with cancer out of clinics and to free up their resources for patients with COVID-19.

Penn provided cancer treatments at home for 1500 patients in 2020 and expects to serve at least that number this year, said Callie Scott, MSc, managing director of the Penn Center for Cancer Care Innovation at the Abramson Cancer Center.

The center administers more than 30 different therapies in the home, including leuprolide, 5-FU, EPOCH, pembrolizumab (Keytruda), nivolumab (Opdivo), bortezomib (Velcade), rituximab (Rituxan), carboplatin, carfilzomib (Kyprolis), cisplatin, cladribine, and cytarabine, Scott said.

Penn’s nurses also administer fludarabine phosphate, ifosfamide (Ifex), interferon alfa-2b, irinotecan, methotrexate sodium, mitoxantrone HCl, omacetaxine mepesuccinate (Synribo), trabectedin (Yondelis), zoledronic acid, denosumab, pegfilgrastim, filgrastim, aldesleukin, cidofovir, and others in patients’ homes.

Handley said Jefferson’s nurses administered in-home infusions of HiDAC and EPOCH to approximately a dozen patients last year and the number is expected to grow. Jefferson’s nurses also have been giving more leuprolide injections at patients’ homes than before the pandemic.

Several other centers have recently launched or expanded home chemotherapy programs, including Fairview Health Services in Minneapolis, Minnesota.12 David M. Gill, MD, an oncologist at Intermountain Healthcare in Salt Lake City, Utah, said he hopes to start providing in-home chemotherapy and immunotherapy in October after delays relating to the pandemic and reimbursement issues. Oncologists at Moffitt Cancer Center in Tampa, Florida, also are considering creating a program, according to a Moffitt spokesperson.

Rogel Cancer Center at University of Michigan Health in Ann Arbor has expanded its HomeMed infusion program, which now serves more than 200 patients.9

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**FIGURE. Innovations in Chemotherapy Treatment**

1-DAY HOSPITAL UNIT/OUTPATIENT CARE

Outpatient hospital unit is reserved for patients requiring short intravenous infusions over a few hours on a daily, weekly, or monthly basis.

MOBILE CHEMOTHERAPY UNITS

Mobile units that deliver chemotherapy treatments beyond the second cycle are introduced in the United Kingdom in 2007.

ORAL CHEMOTHERAPY DRUGS

Chemotherapy drugs are formulated as capsules and tablets.

AMBULATORY CHEMOTHERAPY

The use of portable infusion pumps enables patients to receive continuous infusions lasting up to 7 days outside a hospital or clinic setting.

HOME CHEMOTHERAPY/HOSPITAL-AT-HOME CARE

Intravenous chemotherapy is administered at home under direct medical supervision.

In-Home Infusion Therapy

at a time, according to Tricia Sirois, PharmD, assistant director of pharmacy for home care services.

Some pharmacy companies are encouraging patients with cancer to try home treatment. In November 2020, Optum Infusion Pharmacy, a UnitedHealthcare affiliate, began covering home infusion therapy, including monoclonal antibodies and immunotherapies, for the insurer’s commercial members in Florida. Earlier this year CVS Health’s infusion business, Coram, announced an agreement with Cancer Treatment Centers of America to administer home treatments to eligible patients, starting in Atlanta, Georgia.

In July 2020, health insurer Aetna, a subsidiary of CVS Health, began covering outpatient and home administration of several immune checkpoint inhibitor monotherapies for maintenance regimens, including nivolumab, pembrolizumab, ipilimumab (Yervoy), durvalumab (Imfinzi), cemiplimab (Libtayo), avelumab (Bavencio), and atezolizumab (Tecentriq). The company cited COVID-19–related concerns and potential savings on drug spending and administration exceeding 50%.

Some anticancer regimens are suitable for in-home infusion but others are not, according to a National Comprehensive Cancer Network (NCCN) working group. An NCCN committee, cochaired by Timothy Kubal, MD, MBA, of Moffitt Cancer Center, has been trying since 2015 to make the US chemotherapy delivery system more efficient. The infusion toolkit was revised in light of the pandemic to consider which of 12 regimens currently being provided on an outpatient basis are appropriate for in-home delivery (TABLE16,17).

**SPARSE SAFETY DATA**

Handley said his advocacy for in-home chemotherapy was inspired by Hospital at Home initiatives in the United States and other countries that deploy multidisciplinary care teams to treat patients with congestive heart failure exacerbations, cellulitis, chronic obstructive pulmonary disease flares, or pneumonia. Findings from studies of a 20-year-old program at Johns Hopkins Medicine in Baltimore, Maryland, found that the approach shortened length of stay by one-third, lowered cost relative to usual inpatient care by more than 30%, and demonstrated improved patient satisfaction with the overall care experience.18,19

Many investigators have evaluated the benefits of in-home care in general, but studies focused specifically on home infusion of cancer therapies other than 5-FU are rare, particularly in the United States, and most include small numbers of patients.

Handley and other proponents of home cancer therapy cite a 2012 observational study from Switzerland that analyzed 200 days of home care, representing 46 treatment cycles of intensive chemotherapy in 17 patients.20 Drugs were administered through a portable, programmable pump via an implantable catheter. The main end points were safety, quality of life as measured by the Functional Living Index-Cancer (FLIC), satisfaction of patients and relatives, and cost.

The drugs administered during the study included standard ICE (ifosfamide, carboplatin, and etoposide), modified BEACOPP (etoposide, doxorubicin, cyclophosphamide), BEAM (carmustine, etoposide, cytarabine, and melphalan), VAD (vincristine, doxorubicin, and dexamethasone), melphalan, and other intensive chemotherapy regimens.

Investigators reported that FLIC scores remained constant throughout the study and all patients rated home care as very satisfactory or satisfactory. Patient benefits of home care included increased comfort and freedom, whereas relatives cited better tolerance and less asthenia. An analysis of the mean daily direct costs of care including overhead showed that home care resulted in a 53% cost benefit compared with inpatient hospital treatment (€420 ± 120/day vs €896 ± 165/day), mostly because the use of an automated pump reduced nursing involvement and paraclinical tests.

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<th>TABLE. NCCN Infusion Therapy Update for the COVID-19 Era16</th>
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<td><strong>Regimen</strong></td>
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<td>Blinatumomab</td>
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<td>Cytarabine/daunorubicin liposome induction</td>
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<td>Dose-adjusted EPOCH</td>
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<td>High-dose or intermediate-dose cytotoxic consolidation</td>
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<td>Hyper-CVAD Arm A</td>
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B-ALL, B-cell acute lymphoblastic lymphoma; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ICE, ifosfamide, carboplatin, etoposide phosphate; NCCN, National Comprehensive Cancer Network.

Technical problems complicated 2 cycles of therapy, necessitating hospitalization for a total of 5 days. Three major medical complications (heart failure, angina pectoris, and major allergic reaction) could be managed at home, as could grades 1 and 2 nausea and vomiting, which occurred in 36% of patients.

Scott also cited 2 studies on adverse events (AEs) during home infusion. In one, a retrospective study of implantable venous access devices used at a Veterans Affairs medical center in Arkansas, there were no differences in complications for patients receiving home-based vs hospital-based chemotherapy administration.21 In the other study, investigators evaluated the safety of home administration of adenosine 5′-triphosphate to promote nutritional status and survival in 51 patients with preterminal cancer in the Netherlands.22 They found that the majority of infusions (63%) resulted in no AEs and the AEs that did appear were mild and transient.

In a 2016 analysis of results from 54 studies, investigators found there were often no differences in quality of life or satisfaction or in health care utilization metrics such as emergency room visits, between in-home chemotherapy and hospital or outpatient therapy.23 Any differences that were found were in favor of home care. Findings on financial impact varied according to how costs were calculated and other factors, with some studies finding no difference and others a significant cost benefit for home care over inpatient treatment.

An accompanying analysis of 7 home chemotherapy programs in the United States, Canada, United Kingdom, and Australia found no major safety incidents and high patient and family satisfaction, with 5-FU being the drug offered most frequently.

Connie Sullivan, BSPharm, president and CEO of the National Home Infusion Association (NHIA), said that her organization has been collecting data on AEs during home infusion and will release a report in the next several months. “There is no evidence that patients who do chemotherapy at home have higher rates of adverse events, and they have very high rates of patient satisfaction with the service,” she said.

The lack of robust data has been noted by those opposed to chemotherapy infusion initiated in patients’ homes, including ASCO. “There is a paucity of evidence directly comparing the safety of chemotherapy infusions in the home and outpatient settings. The vast majority of the literature examines home infusion in general, which is of limited utility given the toxicity and hazardous materials specific to chemotherapy,” the ASCO board of directors said in June 2020 position statement.1

“Although ASCO understands the desire for increased flexibility for patients, serious adverse events do occur and require special expertise of oncologists to either prevent or address them during drug preparation and administration,” the directors stated. In voicing their objections in a position statement on home infusion, COA officials stressed the potential for serious AEs. “Home infusion by a provider—who may or may not be a trained oncology nurse—and may not recognize and be prepared to treat any adverse reactions—whether simple, significant, or even lethal—that may occur as a common part of an infusion of cancer drugs is of significant concern,” COA officials said. “It is not an appropriate option for patients with cancer.”

Jefferson and Penn screen patients for suitability, do not give taxanes or other drugs that have a high risk of severe adverse reactions, and administer at least 1 round of therapy in a clinic before approving a patient for home infusion. However, those safeguards are not enough to convince community oncologists such as COA vice president Miriam J. Atkins, MD, FACP, of Augusta Oncology Associates in Georgia.

“It may look good in theory, on paper, but in my office we’ve had patients have severe reactions. We’ve had patients die within a minute of an infusion. Some places are thinking, well, we did the first infusion in the doctor’s office and we’ll do the rest at home. No, because we’ve seen patients do fine with the first 3, and then with the fourth or fifth they have a serious reaction,” Atkins said.

She said that administering therapies at home also deprives patients of important benefits, such as the presence of a physician they can ask about treatment issues and the camaraderie of fellow patients.

“There are many patients who don’t go anywhere, especially during the pandemic. The only place they get to go is my office. They come here and they see the same people. It’s like their chemo club, their community. They talk to each other and also support each other. When you have chemotherapy in the home, it actually just isolates the patient even more, because many patients with cancer feel extremely isolated,” Atkins said.

Atkins, whose practice includes 10 physicians at 3 offices, vowed to fight “tooth and nail” against a shift to home chemotherapy infusion in order to protect patient safety. Whereas patients can interact with oncology nurses during an on-site treatment visit, those who receive therapy at home would not, COA argues.

“Home infusion has inherent limitations in the level of care that can be provided and emergency interventions available to the individuals who are overseeing it,” COA stated. “Even when specifying that the administration of drugs would be by a professional specifically trained to administer...”

“...The goal is really to develop a cancer care delivery system that is more responsive to an individual patient’s needs.”

—NATHAN R. HANDLEY, MD, MBA
these therapies, such individuals could not ensure patient safety without the backup of a team and necessary equipment and supportive drugs.”

Handley contends that the safety issue is overblown. Life-threatening reactions during home infusion are rare and usually occur in the first 30 minutes when a nurse is present, he said. Robust technologies are available to remotely monitor patients and enable quick responses to problems. He argued that existing Hospital at Home programs show that safety concerns are solvable and that the objections actually mask financial concerns or a fear of the unknown.

QUESTIONS OVER COSTS

Although data show that home infusion of therapies for various medical conditions is usually less costly than treatment in a hospital or clinic, Atkins said she believes that paying a specialized oncology nurse to care for 1 patient at a time raises costs and makes reimbursement difficult.

“I know UPenn has a deep pockets. They could probably do whatever they want to do. But in reality patients have Medicare, possibly Medicaid, and some private insurance. [Those payers] are not going to want to pay for a certified nurse. Chemo nurses are not inexpensive. To have 1 nurse sit with a patient for 5 or 6 hours—because some drugs take that long—is a waste of resources,” she said.

The financial implications of converting patients to in-home chemotherapy infusion are complex and can vary depending on several factors.

Handley said home infusion is less expensive than on-site administration when the fixed costs of operating an infusion clinic are included in the calculations. In addition, a well-developed, moderate-volume home-based system allows agile adjustment of nurse staffing that boosts efficiency and keeps labor costs down, he said. At the same time, some payers provide lower reimbursements for in-home care, which results in less health care spending overall but can create financial difficulties for providers.

“Lower costs may mean lower reimbursement, and the delta between how much things cost and how much you get paid is not always favorable. That’s the tricky situation we talk about,” Handley said.

A concern among independent practices is that the movement toward more home infusion threatens not only to cut into their revenues but also to take away control over their patients’ care. For example, an insurer could mandate home chemotherapy to cut costs and require members to use medication and nurses from its own specialty pharmacy, COA executive director Ted Okon said.

“You could see them saying, first of all, here’s the restricted formulary or step therapy, and we have to administer the drug to the patient in their home,” he said. “You’ve got the insurer/specialty pharmacy making the decision on the drug—not only who’s going to administer it but how it’s going to be administered and where. That’s a very, very scary thought.”

Sullivan said she was “a little bit perplexed” by the intense opposition to home infusion from some oncologists, adding that she believes business concerns are driving some of the objections. The infusion providers she represents are not clamoring to take over chemotherapy administration from practices, she said, but they do have many years of training and experience in administering drugs to patients with cancer, including some chemotherapies, and they are well qualified to safely give a range of therapies if asked.

Meanwhile, the use of some types of in-home chemotherapy could grow if Congress passes proposed legislation that would broaden Medicare coverage of home infusion in general.

The 21st Century Cures Act of 2016 added a new home infusion services benefit to Medicare Part B, but CMS has interpreted the benefit as requiring a nurse to be physically present in the patient’s home in order for providers to be reimbursed.24

NHIA says because the interpretation does not account for remote services, provider participation in the Medicare benefit has dropped over the past several years. The proposed Preserving Patient Access to Home Infusion Act would remove the physical presence requirement and require CMS to pay home infusion providers for each day drugs are administered.

However, the Medicare Part B benefit focus on drugs delivered through pumps and covers only 8 cancer drugs.25 Handley said the legislative proposals he has seen would not have a major impact on in-home chemotherapy programs such as those at Penn and Jefferson.

For a full list of references, see the article at OncLive.com.
IN HER2+ EARLY BREAST CANCER (EBC), UNDERSTAND HER RISK OF RECURRENCE

HER2=human epidermal growth factor receptor 2.
HER RISK OF RECURRENCE REMAINS, EVEN AFTER NEOADJUVANT TREATMENT

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.1,2

The CTNeoBC pooled-analysis assessed the risk of recurrence following neoadjuvant treatment among patients with breast cancer, including HER2+ EBC, based on historic data1

The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.1

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.1
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease. This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery. Association between pCR and event-free survival (EFS)* in the HER2+ subgroup analysis of the CTNeoBC study

1,989 patients with HER2+ tumors were included in the subgroup analysis. 55% of which did not receive a full year of adjuvant HER2-targeted monotherapy treatment.

While there are different paths you can choose for your patient with HER2+ EBC, her treatment shouldn’t stop at neoadjuvant therapy.

*EFS was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.
Discover possible adjuvant treatment options that may be right for her*:

For patients who achieve pCR, visit PCRinEBC.com

For patients who do not achieve pCR, visit NoPCRinEBC.com

*There may be other treatment options available for your patients.

Experts Review Key Data From ESMO Congress 2021

by BRITTANY LOVELY

NEARLY 2000 ABSTRACTS WERE included in the proceedings at the European Society for Medical Oncology (ESMO) Congress 2021. The data presented in late-breaking abstracts, at presidential symposia, and during poster sessions have contributed to the evolving treatment landscape across the continuum of care.

During the meeting, OncologyLive® spoke with several leading experts on a variety of tumor types, each of whom highlighted those abstracts set to influence the next wave of investigative directions and change the standard of care for patients.

Full abstracts are available for reference at bit.ly/3DAhEla.

LUNG CANCER

LBA9
IMpower010: Sites of relapse and subsequent therapy from a phase III study of atezolizumab vs best supportive care after adjuvant chemotherapy in stage IB-IIIA NSCLC

In the phase 3 IMpower010 trial (NCT02486718), 1005 patients with completely resected stage IB to IIIA non-small cell lung cancer NSCLC were randomized 1:1 to receive either 1200 mg of atezolizumab (Tecentriq) every 21 days or best supportive care following 1 to 4 cycles of cisplatin plus pemetrexed, gemcitabine, docetaxel, or vinorelbine. Atezolizumab extended the disease-free survival benefit in patients in the all-randomized stage II to IIIA population with PD-L1 expression on at least 50% of tumor cells (TC; HR, 0.43; 95% CI, 0.27-0.68).

In findings from a subgroup analysis, adjuvant treatment with atezolizumab provided a modest disease-free survival benefit for patients with TC 1% to 49% (HR, 0.87; 95% CI, 0.60-1.26) in all-comers including those with EGFR or ALK mutations. These results confirmed that the benefit observed in the TC 1% or higher population (HR, 0.66; 95% CI, 0.50-0.88) was primarily driven by those with TC 50%. Based on these data, atezolizumab was approved for the adjuvant treatment of patients with PD-L1 expression on at least 1% of tumor cells in October.

“One abstract of particular interest for me [concerned] the [IMpower010] data. We had previously seen [results of this] study, but one thing that was really missing was the subgroup analysis by PD-L1 expression. It was clear, prior to ESMO, that patients with...”
stage II and III disease and PD-L1 of at least 50% would benefit. However, the analysis was of the 1% or greater population not 1% to 49%, leaving open the question of whether the benefit in the 1% or greater population was entirely driven by those who were 50% or greater or whether the patients with 1% to 49% actually derived benefit.

At ESMO 2021 I was very pleased to see this subgroup analysis. It had a trend in the right direction which for me is good enough, because I’ll remind everyone that the study wasn’t powered to address that subgroup analysis.

LBA47
Activity of OSE-2101 in HLA-A2+ non–small cell lung cancer (NSCLC) patients after failure to immune checkpoint inhibitors (IO): Final results of phase III Atalante-1 randomised trial

The final results of the phase 3 ATALANTE 1 trial (NCT02654587) demonstrated that use of the anticancer neo-epitope–based vaccine OSE2101 (Tedopi) resulted in a statistically improved survival benefit as treatment for patients with advanced or metastatic NSCLC with secondary resistance to platinum-based chemotherapy and immunotherapy (combined or sequenced).

Specifically, the median overall survival (OS) for patients who received the vaccine (n = 80) was 11.1 months (95% CI, 8.6-13.5) compared with 7.5 months (95% CI, 4.7-10.3) for those who received standard of care (n = 38; HR, 0.59; 95% CI, 0.38-0.91; P = .017). Of patients who experienced disease progression, those who received OSE2101 had a greater delay in the time of progression to death compared with standard of care. The median postprogression OS was 7.7 months (95% CI, 5.6-9.7) in the experimental arm vs 4.6 months (95% CI, 3.1-5.8) in the control arm (HR, 0.46; 95% CI, 0.27-0.79; P = .004).

Based on these data, investigators concluded that the benefit to risk ratio was favorable for OSE2101 for this patient population who do not have therapeutic alternatives.

“Tere were a lot of abstracts that are of relevance to research even if they are not reaching clinical practice. One that is not being discussed as much, but that I found interesting, concerns the one with data on OSE2101, a human leukocyte antigen vaccine targeting 5 tumor associated antigens, compared with docetaxel.

I don’t know if these data will result in approved use, but for those interested in personalized immunotherapy I think it gives one heart that a vaccine approach done right could yield fruit. When you think about other approaches being taken to personalize treatments with advanced bioinformatics sequencing and improvements in adjuvant treatment options and other aspects of vaccination, I think it adds a little wind to the sails that this approach may ultimately be something that helps patients.”

1254P
Efficacy and safety of tepotinib in patients (pts) with advanced age: VISION subgroup analysis of pts with MET exon 14 skipping NSCLC

Investigators observed robust and durable clinical activity in patients with non–small cell lung cancer with MET exon 14 skipping treated with tepotinib in the phase 2 VISION trial (NCT02864992). Among 275 patients who received no more than 2 lines of prior therapy, the overall response rate (ORR) was 49.1% (95% CI, 43.0%-55.2%), the median duration of response was 13.8 months (95% CI, 9.9-19.4), and the median progression-free survival was 10.8 months (95% CI, 8.5-12.4).

When stratified by age (< 75 years [n = 157] vs ≥ 75 years [n = 118]), the ORRs were 52.2% (95% CI, 44.1%-60.3%) vs 44.9% (95% CI, 35.7%-54.3%), respectively. The median duration of response was 12.4 (95% CI, 9.5-32.7) vs 13.8 months (95% CI, 9.0-not estimable), and median progression-free survival was 11.0 (95% CI, 8.2-13.7) vs 10.4 months (95% CI, 8.2-13.7). The investigators concluded that continued exploration of tepotinib and other novel targeted therapies directed against MET exon 14 skipping should be prioritized for the treatment of patients of advanced age.

“This is a very rare target, and we must be aware that the target can be present not just in adenocarcinoma but also in other histologies. It is important to also remember that patients can have a very long-lasting response with MET inhibitors, in this case with tepotinib. The drug is feasible as a treatment in older populations and clearly is much better than chemotherapy.”
LBA61
Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study

Results from an updated analysis of the phase 3 CASPIAN trial (NCT03043872) showed that the addition of durvalumab (Imfinzi) to platinum-etoposide maintained a significant survival benefit in patients with extensive-stage small cell lung cancer (ES-SCLC) vs platinum-etoposide alone. At the 3-year follow-up the median overall survival (OS) was 12.9 months (95% CI, 11.3-14.7) vs 10.5 months (95% CI, 9.3-11.2), respectively (HR, 0.71; 95% CI, 0.60-0.86; \( P = .0003 \)). The 3-year OS rates were 17.6% vs 5.8%, respectively.

The investigators noted that with 3 times more patients estimated to be alive at 3 years when treated with the anti-PD-L1 chemotherapy combination, the regimen should be considered the first-line standard of care for patients with ES-SCLC.

“I want to emphasize the fact that trials, in particular immunotherapy trials, should be followed up long term. I understand that hazard ratio is very important, median survival is very important, and [these are end points] that lung cancer physicians are used to. But here we have a new dimension, which is the long-term benefit [and] the potential for cure. This trial and others are opening the door to something that we didn’t ask or talk about in the past with our patients.”

GASTROINTESTINAL CANCER

LBA6
KRYSIAL-1: Adagrasib (MRTX849) as monotherapy or combined with cetuximab (Cetux) in patients (Pts) with colorectal cancer (CRC) harboring a KRAS G12C mutation

Investigators in the phase 1/2 KRYSIAL-1 trial (NCT03785249) assessed the efficacy of the novel KRAS G12C inhibitor adagrasib in patients with solid tumors harboring the mutation. The efficacy results for those with colorectal cancer showed that the agent elicited a 22% response rate among patients treated with the agent as a monotherapy, including 1 unconfirmed partial response.

Further, 64% of patients had stable disease and investigators observed clinical benefit in 87% of patients. The median duration of response was 4.2 months (range, 2.3-6.9) and at the data cutoff of May 25, 2021, 40% of patients remained on treatment.

In the efficacy population (n = 46) for progression-free survival (PFS) analysis the median PFS was 5.6 months (95% CI, 4.1-8.3), with a 6-month PFS rate of 42%.

For patients treated with adagrasib in combination with cetuximab (Erbitux; n = 28), the response rate was 43% including 2 unconfirmed partial responses. The investigators observed stable disease in 57% of patients and reported that clinical benefit was observed in 100% of treated patients. At data cutoff of July 9, 2021, 71% of patients remained on treatment.

“The story in colorectal cancer is [all about the] KRAS G12C mutation and there are some promising approaches. As studies mature and get larger, that is an important one.”

LBA54
Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastatic esophagogastric adenocarcinoma (EGA): Results of the randomized phase II INTEGA trial (AIO STO 0217)

Investigators evaluated 2 experimental first-line treatment options in the phase 2 INTEGA trial (NCT03409848) for patients with HER2-positive advanced or metastatic esophagogastric adenocarcinoma. Patients were randomized to receive either trastuzumab (Herceptin) plus nivolumab...
(Opdivo) plus ipilimumab (Yervoy) or trastuzumab and nivolumab in combination with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX). Each arm had 44 patients. The overall response rate was 56% in the FOLFOX arm compared with 32% in the immunotherapy triplet arm. The median progression-free survival was 10.7 months vs 3.2 months, respectively.

Investigators concluded that both treatment arms were feasible treatment options for this patient population; however, the FOLFOX regimen was favored across outcomes including median overall survival (21.8 vs 16.4 months, respectively), overall survival at 12 months (70% vs 57%), and progression-free survival rate at 12 months (37% vs 15%). This benefit was maintained in subgroup analysis by combined positive score and HER analysis by central review.

“In the HER2 space for gastroesophageal cancer there are a lot of exciting, targeted therapies coming through [that are] trying to build on chemotherapy plus trastuzumab with or without immunotherapy. I think that those strategies are also going to be promising in the future.”

BREAST CANCER

LBA16
KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC

The addition of pembrolizumab (Keytruda) to chemotherapy in the first-line setting elicited clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) for patients with PD-L1–positive (combined positive score [CPS] ≥ 10), metastatic triple-negative breast cancer (TNBC) vs placebo plus chemotherapy. The data met the primary end points of the phase 3 KEYNOTE-355 trial (NCT02819518).

Specifically, the median OS in the intention-to-treat population with pembrolizumab (n = 566) was 17.2 months vs 15.5 months with placebo (n = 281; HR, 0.89; 95% CI, 0.76-1.05). The 2-year OS rates were 35.5% vs 30.4%, respectively. The median PFS was 7.5 months in the investigative arm compared with 5.6 months in the placebo arm (HR, 0.82; 95% CI, 0.70-0.98), and 1-year PFS rates were 29.3% vs 20.8%.

When stratified by CPS, pembrolizumab demonstrated the greatest benefit in patients with CPS of 10 or greater. The median OS for patients who received pembrolizumab (n = 220) was 23.0 months vs 16.1 months for those who received placebo (n = 103; HR, 0.73; 95% CI, 0.55-0.95; one-sided P = .0093). The 2-year OS rates were 48.2% vs 34.0%, respectively. The median PFS was 9.8 months with pembrolizumab vs 5.6 months with placebo (HR, 0.66; 95% CI, 0.50-0.88), with a 1-year PFS rate of 39.1% vs 23.0%, respectively.

“It’s great to see a survival advantage. It’s interesting to me that the survival difference was similar to what was shown in IMpassion130 [NCT02425891]; however, IMpassion130 had a different statistical design, which was hierarchical, and because they didn’t show a survival benefit in the intention-to-treat population, [investigators] weren’t allowed to assess formal statistical differences in the PD-L1–positive population. So it brings up the question: If you had a patient who was [PD-L1] positive via SP142 [Ventana PD-L1 assay], what would you do? Because of the unfortunate design and negative results from IMpassion131 [NCT03125902], Roche withdrew the indication for atezolizumab (Tecentriq) in the United States because they did not have confirmatory data. Right now, I would treat these [US patients] with pembrolizumab because I think those patients would benefit. I do think this is a new standard of care. It’s critical that patients, staff, and physicians be educated about how to recognize immune-related toxicities as early as possible and institute treatment that I think really makes a big difference. It is important to keep in mind that we are only benefitting 40% of our patients, so we need more treatments and [we need to] encourage enrollment in clinical trials that are looking at combination therapies and novel agents to improve outcomes for patients with TNBC.”
KEY ELIGIBILITY CRITERIA:

- Diagnosis of Metastatic Non-small Cell Lung Cancer
- Disease progression after 1 or more lines of prior therapy which may have been a checkpoint inhibitor
- PD-L1 positive or negative status
- Tumors with EGFR, ALK, ROS mutations acceptable
- ECOG PS 0 – 1 (Fully active or able to carry out light work or activity)
- At least one tumor that can be safely removed by surgery for TIL and a second measurable tumor for response assessment

If these key eligibility criteria are met, you may be eligible to participate in our clinical study program. There are additional eligibility criteria that must be met and can only be assessed by a study physician.

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and effectiveness of this study has not been determined.

FOR MORE INFORMATION

CALL CENTER 1-866-565-4410, select option 3
EMAIL clinical.inquiries@iovance.com

CLINICALTRIALS.GOV
Lung Trial: NCT04614103
Solid tumor trial NSCLC cohorts: NCT03645928

LN-145 (TUMOR INFILTRATING LYMPHOCYTES; TIL) is an investigational, personalized immunotherapy derived from the patient’s own immune cells.
LBA1
Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): results of the randomized phase 3 DESTINY-Breast03 study

One of the highly anticipated studies presented at ESMO 2021 was the late-breaking abstract highlighting data from the Destiny-Breast03 trial (NCT03529110), the first head-to-head study of fam-trastuzumab deruxtecan-nxki (Enhertu) vs ado-trastuzumab emtansine (T-DM1; Kadcyla) for patients with advanced HER2-positive metastatic breast cancer previously treated with trastuzumab (Herceptin) and taxane.

Results showed that the median progression-free survival (PFS) for patients treated with trastuzumab deruxtecan was not reached (95% CI, 18.5-not estimable [NE]) vs 6.8 months (95% CI, 5.6-8.2) with T-DM1 (HR, 0.28; 95% CI, 0.22-0.37; \(P = 7.8 \times 10^{-22}\)). Among the 261 patients in the trastuzumab deruxtecan arm the 12-month PFS rate was 75.8% (95% CI, 69.8%-80.7%) vs 34.1% (95% CI, 27.7%-40.5%) among 263 patients treated in the T-DM1 arm. In a discussion of the data during the meeting, investigator Shanu Modi, MD, said, “If the waterfall plot from DESTINY-Breast01 [NCT03248492] was dramatic, I think these PFS curves from DESTINY-Breast03 are startling.”

Further, the median overall survival (OS) was NE in both arms (HR, 0.56; 95% CI, 0.36-0.86; \(P = .007172\)). The 12-month OS rates were 94.1% (95% CI, 90.3%-96.4%) in the trastuzumab deruxtecan arm vs 85.9% (95% CI, 80.9%-89.7%), in the T-DM1 arm.

“DESTINY-Breast03 reflects impressive activity of trastuzumab deruxtecan as second-line therapy for HER2-positive metastatic breast cancer, relative to current standard of care T-DM1. With higher rates of interstitial lung disease and established efficacy of trastuzumab deruxtecan after T-DM1 based on DESTINY-Breast01, it remains to be seen which patients benefit from trastuzumab deruxtecan in the second line vs later.”

GYNECOLOGIC CANCER

LBA33
Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial

In the double-blind, phase 3 OReO study (NCT03106987), patients with nonmucinous platinum-sensitive relapsed ovarian cancer were retreated with the PARP inhibitor olaparib (Lynparza) 300 mg or placebo until disease progression. Results showed that rechallenge with maintenance olaparib following disease progression with a PARP inhibitor and a complete or partial radiological response to subsequent treatment with platinum-based chemotherapy improved progression-free survival (PFS) vs placebo regardless of BRCA mutation status.

For patients with BRCA-mutant disease the median PFS was 4.3 months for those who received olaparib (n = 74) vs 2.8 months with placebo (n = 38; HR, 0.57; 95% CI, 0.37-0.87; \(P = .022\)). The 12-month PFS rate in this
patient population was 19% vs 0%, respectively. In the cohort of patients without BRCA mutations, the median PFS for those who received olaparib (n = 72) was 5.3 months vs 2.8 months with placebo (n = 36; HR, 0.43; 95% CI, 0.26-0.71; P = .0023). The 12-month PFS rates were 14% vs 0%, respectively.

“[Data from the] OReO trial showed the benefit of PARP inhibitors in platinum-sensitive recurrence in the maintenance setting. These improvements were modest, however [results] did show that one of the best predictors of PARP responsiveness is the responsiveness to platinum.

We need a lot more information from this trial...as very small numbers of responsiveness may be driving the overall hazard ratio. For example, what wasn’t presented was the number of patients who had discontinued prior PARP exposure because of toxicity vs those who discontinued because of progression or they completed therapy; in other words, 2 years with the SOLO-1 [regimen (NCT01844986)] or 3 years with the PRIMA [regimen (NCT02655016)]. The patient who does not experience progression on PARP vs the patient who progresses seem to be much different patient populations and we need to get more information.”

MELANOMA

Jason Luke, MD
Associate Professor of Medicine
Division of Hematology/Oncology
Director of the Cancer Immunotherapeutics Center
University of Pittsburgh Medical Center Hillman Cancer Center Cancer Immunology and Immunotherapy Program
Pittsburgh, PA

LBA3_PR
Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial

Patients with high-risk stage II melanoma saw a significant reduction in the risk of disease recurrence or death when treated with adjuvant pembrolizumab compared with placebo, according to results of the phase 3 KEYNOTE-716 trial (NCT03553836). Median recurrence-free survival (RFS) was not reached in either arm (HR, 0.65; 95% CI, 0.46-0.92; P = .00658). The 12-month RFS rate was 90.5% among 487 patients who received adjuvant pembrolizumab vs 83.1% for the 489 patients who received placebo.

“KEYNOTE-716 is very early in its data maturation and there are a lot of patients who haven’t had recurrence events. Despite having quite a substantial benefit that will likely change practice in terms of RFS, we expect that the benefit will increase over time. We are seeing a 35% benefit in terms of reducing recurrence [and] I fully expect that number is going to go up over time as more events happen in the clinical trial.

Another really important aspect of this trial is that it has 2 parts: the first part is the adjuvant treatment, and the second part is the crossover. Following patients and seeing what happens to them after they have recurrence events and go on to other therapies is an absolutely essential part of this clinical trial. [This way] we can better understand the long-term implications of these clinical data and what happens to these patients in these scenarios because we haven’t had this before.

There were some naysayers when we started this trial [who said] that [patients with] stage IIB and IIC disease were too low risk to treat in a clinical trial. I think these results really emphasize that patients with those disease stages truly are at high risk for rapid and distant metastatic recurrence. Treatment with pembrolizumab improves that situation quite substantially. I think this treatment should be offered to all patients with stage IIB and IIC and we should stop thinking about nonmodal melanoma as low risk; in fact, it is high risk and these patients deserve the opportunity to be treated.”
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. 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.

*Study design:* Phase 2 open-label, single-arm trial (N=145) to evaluate the efficacy and safety of ZYNLONTA as a monotherapy in r/r DLBCL after 2 or more systemic therapies. Patients received 0.15 mg/kg Q3W for 2 cycles with dexamethasone premedication (unless contraindicated), then 0.075 mg/kg Q3W for subsequent cycles. Primary endpoint was ORR, evaluated by independent review committee using Lugano 2014 criteria. ZYNLONTA was administered until progressive disease or unacceptable toxicity.¹

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Effusion and Edema** Serious effusion and edema occurred. Grade 3 edema: 3% (primarily peripheral edema or ascites); Grade 3 pleural effusion: 3%; Grade 3/4 pericardial effusion: 1%. Monitor patients for new/worsening edema or effusions. Withhold ZYNLONTA for Grade >2 until toxicity resolves. Consider diagnostic imaging in patients with symptoms of pleural or pericardial effusion, such as new/worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management.

**Myelosuppression** Serious or severe myelosuppression—including neutropenia, thrombocytopenia, and anemia—occurred. Grade 3/4 neutropenia: 32%; thrombocytopenia: 20%; anemia: 12%. Grade 4 neutropenia: 21%; thrombocytopenia: 7%. Febrile neutropenia occurred: 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA.

**Adverse Reactions** Consider prophylactic granulocyte colony-stimulating factor administration as applicable. **Infections** Fatal and serious infections, including opportunistic infections, occurred. Grade ≥3: 10%; fatal infections: 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new/worsening signs or symptoms consistent with infection. For Grade 3/4 infection, withhold ZYNLONTA until infection has resolved.

**Cutaneous Reactions** Serious cutaneous reactions occurred. Grade 3: 4%, including photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new/worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for Grade 3 until resolution. Advise patients to: minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows; protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, consider dermatologic consultation.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to ADC Therapeutics at 1-855-690-0340.

**AR** = adverse reaction; **CI** = confidence interval; **CR** = complete response; **DOR** = duration of response; **ORR** = overall response rate; **NE** = not estimable; **PR** = partial response; **r/r** = relapsed or refractory
Challenge expectations in 3L DLBCL

Take the next step...

...on the path to response with the first and only single-agent, CD19-directed ADC

48.3% ORR\(a\)\(b\)\(c\)
(95% CI: 39.9, 56.7)\(^1\)

24.1% CR; 24.1% PR\(^2\)
(95% CI for each: 17.4, 31.9)\(^1\)

1.3 Months
median time to response
(range: 1.1–8.1)\(^1\)

Single-Agent IV\(^1\), \(^b\)
30-minute infusion
Once every 3 weeks

\(a\) Median duration of response: 10.3 months (95% CI: 6.9, NE). Of 70 patients with objective response, 25 (36%) were censored prior to 3 months; 26% of responders had a DOR of ≥6 months.\(^1\)

\(b\) Premedication: dexamethasone 4 mg (oral or IV) twice daily for 3 days, beginning the day before infusion. If dexamethasone administration does not begin the day before ZYNLONTA, it should begin at least 2 hours prior to ZYNLONTA infusion (unless contraindicated).\(^1\)

\(c\) Median follow-up time: 7.3 months (range: 0.3–20.2).\(^1\)

Embryo-Fetal Toxicity ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

ADVERSE REACTIONS In a pooled safety population (215 patients, Phase 1 and LOTIS-2), the most common (>20%) ARs, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase (GGT), neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

In LOTIS-2, serious ARs occurred in 28% of patients. The most common (>2%) were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal ARs: 1%, due to infection.

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

www.zynlontahcp.com
ZYNLONTA® (loncastuximab tesirine-lpyl) for injection, for intravenous use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

INDICATIONS AND USAGE
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. 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
Effusion and Edema. Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression. Treatment with ZYNLONTA can cause severe or serious myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections. Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions. Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatological consultation should be considered.

Embryo-Fetal Toxicity. Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects 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 ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA, and for 6 months after the last dose (see Use in Specific Populations (8.1, 8.3)).

ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Effusion and Edema
- Myelosuppression
- Infections
- Cutaneous Reactions
- Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADC-T042-001 (LOTIS-2) and ADC-T042-010, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles. In this pooled safety population of 215 patients, the most common (≥20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia,

Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYNLONTA (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>38</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rashb</td>
<td>30</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
</tr>
<tr>
<td>Abdominal paina</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal paina</td>
<td>23</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspneaa</td>
<td>13</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>10</td>
</tr>
</tbody>
</table>

References:

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**Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYNLONTA (N=145)</th>
<th>All Grades (%)</th>
<th>Grades 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>38</td>
<td>1a</td>
<td></td>
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<tr>
<td>Edema</td>
<td>28</td>
<td>3a</td>
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<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
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<td></td>
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<tr>
<td>Rash</td>
<td>30</td>
<td>2a</td>
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<tr>
<td>Pruritus</td>
<td>12</td>
<td>0</td>
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<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
<td>2a</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
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<td></td>
<td></td>
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<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>2a</td>
<td></td>
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<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
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<tr>
<td>Constipation</td>
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<td>Musculoskeletal and Connective Tissue Disorders</td>
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<td>Musculoskeletal pain</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
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<td>Dyspnea</td>
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<tr>
<td>Pleural effusion</td>
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<td>2a</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
<td>&lt;1a</td>
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</tr>
</tbody>
</table>

Clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA included:

- Blood and lymphatic system disorders: Fever, neutropenia (3%)
- Cardiac disorders: Pericardial effusion (3%)
- Infections: Pneumonia (5%), sepsis (2%)
- Skin and subcutaneous disorders: Hyperpigmentation (4%)
- General disorders: Infusion site extravasation (<1%)

**Table 2: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYNLONTA*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>58</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>52</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>51</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>57</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>48</td>
</tr>
<tr>
<td>AST increased</td>
<td>41</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
</tr>
<tr>
<td>ALT increased</td>
<td>34</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value.

No Grade 4 adverse reactions occurred

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. 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 outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

**Data**

**Animal Data**

Animal reproductive or developmental toxicity studies were not conducted with loncastuxizam teseine-ipl. The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

**Lactation**

**Risk Summary**

There is no data on the presence of loncastuxizam teseine-ipl or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

**Females and Males of Reproductive Potential**

ZYNLONTA can cause fetal harm when administered to pregnant women.

**Pregnancy Testing**

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

**Contraception**

*Females* Advise women of reproductive potential to use effective contraception during treatment and for 9 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 the treatment with ZYNLONTA and for 6 months after the last dose.

**Infertility**

*Males* Based on the results from animal studies, ZYNLONTA may impair fertility in males. The effects were not reversible in male cynomolgus monkeys during the 12-week drug-free period.

**Pediatric Use**

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

**Geriatric Use**

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

**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). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).

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Datopatamab Deruxtecan Appears to Leverage TROP2 Expression in NSCLC

by KYLE DOHERTY

A VOID IN THE treatment landscape exists for patients with advanced non-small cell lung cancer (NSCLC) who receive 1 to 2 lines of prior therapy as the average overall survival (OS) is less than 1 year.1 TROP2 expression is associated with a poor prognosis, particularly in patients with adenocarcinoma histology, and offers a promising target for treatments.2,3

Investigators aim to expand the treatment portfolio for this patient population with the initiation of the phase 3 TROPION-LUNG01 trial (NCT04656652). The trial is designed to examine the TROP2-directed antibody-drug conjugate (ADC) datopotamab deruxtecan (DS-1062) vs docetaxel in patients with advanced or metastatic NSCLC without actionable genomic alterations who have previously received platinum-based chemotherapy and immunotherapy.4

“TROP2 is a glycoprotein that is expressed on many bacterial tissues and is highly overexpressed in cancers,” explained Solange Peters, MD, PhD, head of the Medical Oncology Department and of specialized consultation for thoracic tumors at Lausanne University Hospital in Switzerland, in an interview with OncologyLive®. “TROP2 is strongly overexpressed on cancer tissue as compared [with] normal tissue by a very high magnitude of difference [and it] is a negative prognostic factor—the more TROP2, the shorter the lifespan of the patients. It was chosen as a target in the development of datopotamab deruxtecan [because of] its overexpression,” said Peters, who also serves as the physician in charge of the Thoracic Tumor Center at the hospital and is an associate professor at the University of Lausanne.

Datopotamab deruxtecan is an ADC that replicates the payload of fam-trastuzumab deruxtecan-nxki (Enhertu) but with a lower drug to antibody ratio (4:1). Specifically, the agent comprises a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody attached to a topoisomerase I inhibitor via a stable tetrapeptide-based cleavable linker.5

“Each antibody is going to the target with the 4 molecules of chemotherapy…. [This is] chemotherapy that one wouldn’t like to administer intravenously because it’s very toxic,” Peters said. “As soon as it’s bound, it will release… the 4 molecules of chemotherapy into the microenvironment of the cancer cell. It will also affect the cancer cells beside it, which didn’t or cannot bind the antibody.”

**FIGURE. Phase 3 InPACT Trial (NCT02305654)**

**Eligibility criteria**

- 18 years or older
- Life expectancy of ≥ 3 months
- Pathologically documented stage IIIB, IIIC, or IV NSCLC with no EGFR or ALK alterations and no known ROS1, NTRK, BRAF, or other actionable driver oncogenes
- ≥ 1 prior therapy for advanced or metastatic NSCLC
- Documentation of radiographic disease progression on or after most recent treatment regimen for advanced NSCLC
- ECOG performance status of 0 to 1
- Adequate bone marrow, hepatic, and renal function within 7 days before cycle 1, day 1

**End points**

- **Primary**
  - PFS by BICR
  - OS
- **Secondary**
  - PFS by investigator
  - ORR
  - DOR
  - DCR
  - TTR
  - QOL

**BICR, blind independent central review; DOR, duration of response; IV, intravenously; NSCLC, non–small cell lung cancer; ORS, overall response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TTR, time to response.

*All inclusion criteria must be met within 28 days of randomization into the study.*

**EARLY DATA ESTABLISH ROLE FOR DATOPOTAMAB DERUXTECAN**

Investigators have evaluated datopotamab deruxtecan monotherapy in the ongoing phase 1 TROPION-PanTumor01 trial (NCT03401385). The dose-escalation and -expansion study includes a large cohort of adult patients with advanced or metastatic NSCLC. It also includes cohorts of patients with other tumor types, such as hormone receptor-positive, HER2-negative triple-negative breast cancer. The primary end points of the study are establishing a maximum-tolerated dose (MTD) and safety. Efficacy and pharmacokinetics are secondary end points.5,6

During the trial’s dose-escalation phase, patients with NSCLC received datopotamab deruxtecan at 0.27 mg/kg to 10 mg/kg once every 3 weeks. The MTD was 8 mg/kg once every 3 weeks. In the dose-expansion phase, patients in the NSCLC cohort received the agent at doses of 4 mg/kg (n = 50), 6 mg/kg (n = 50), and 8 mg/kg (n = 80).6

At the data cutoff of April 6, 2021, patients who received the 6-mg/kg dose had the best overall response rate (ORR) at 28%; all responses were partial responses. The median duration of response (DOR) was 10.5 months (95% CI, 5.6-not evaluable [NE]).6 Patients who received the 4-mg/kg dose had an ORR of 24%; the median DOR was NE (95% CI, 2.8-NE). Those who received the 8-mg/kg dose also had an ORR of 24%, with 1 patient experiencing a complete response. The median DOR was 9.4 months (95% CI, 5.8-NE). 6

“The first waterfall plots are very exciting.
Eligible patients must have a life expectancy of at least 3 months, measurable disease based on local imaging assessment, and an ECOG performance status of 0 to 1 at screening. Patients also need to have adequate blood clotting function, a left ventricular ejection fraction of at least 50%, and adequate bone marrow, hepatic, and renal function 7 days prior to day 1 of cycle 1. All inclusion criteria must be met within 28 days of randomization.

Patients previously treated with a TROP2-targeted therapy, docetaxel as monotherapy or in combination with other agents, or any agent containing a chemotherapeutic agent targeting topoisomerase I are ineligible for enrollment. Patients with NSCLC who are eligible for definitive local therapy alone, who have uncontrolled or significant cardiovascular disease, or who have leptomeningeal carcinomatosis or metastasis will also be excluded.

The primary end points are progression-free survival (PFS) by blinded independent central review per RECIST 1.1 and OS. Secondary end points include investigator-assessed PFS, ORR, DOR, disease control rate, and time to response. The estimated study completion date is June 27, 2024.

“Datopotamab deruxtecan will [likely] fit into the second-line [treatment] strategies because we have already seen in fragile patients that it’s better than what we observe in fit patients in the second line with docetaxel,” Peters concluded. “Will it give some more visibility of the cancer cell and the cancer cell death in the immune system, allowing for a long-term benefit, as we like to see in immunotherapy? We’ll have to see if it’s feasible in terms of toxicity profile and, more importantly, if it’s durable in terms of efficacy. Otherwise, if you just have an additive phenomenon, you always have to think about sequencing. As soon as we see something synergistic, multiplying the beneficial effect, then [datopotamab deruxtecan] may become a frontline strategy.”

REFERENCES

THE ADDITION OF PEMBROLIZUMAB (Keytruda) to chemotherapy with or without bevacizumab (Avastin) elicited a clinically meaningful and significant survival benefit for patients with persistent, recurrent, or metastatic cervical cancer and may represent a new standard of care for this population, according to Bradley J. Monk, MD, FACS, FACOG.

The practice-changing data come from the phase 3 KEYNOTE-826 (NCT03635567) presented at the European Society for Medical Oncology Congress 2021, which showed benefit in progression-free survival (PFS) and overall survival (OS) with the addition of pembrolizumab.1 Specifically, results from the all-comer population showed that patients in the pembrolizumab plus chemotherapy with or without bevacizumab cohort (n = 308) had a median PFS of 10.4 months (95% CI, 9.1-12.1) compared with 8.2 months (95% CI, 6.4-8.4) for those in the chemotherapy with or without bevacizumab cohort (n = 309; HR, 0.65; 95% CI, 0.53-0.79; P < .001). The median OS was 24.4 months (95% CI, 19.2-not reached) in the investigative arm vs 16.5 months (95% CI, 14.5-19.4) in the control arm (HR, 0.67; 95% CI, 0.54-0.84; P < .001). Additional data showed that the benefit was observed across all protocol-specified subgroups with the addition of the PD-1 inhibitor (TABLE1).

On October 13, the FDA approved pembrolizumab in combination with chemotherapy for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 combined positive score of at least 1 based on the data from this trial.2

In an interview with OncologyLive®, Monk contextualizes how investigators arrived at this juncture in the treatment landscape for this patient population and notes the key studies that served as pivotal landmarks. Monk, an investigator of the KEYNOTE-826 trial, is director and professor in the Division of Gynecologic Oncology at Arizona Oncology, University of Arizona College of Medicine, Creighton University School of Medicine at St. Joseph’s Hospital; medical director of the gynecologic oncology research for the US Oncology Network; and codirector of Gynecologic Oncology Group (GOG) Partners.

How does the KEYNOTE-826 study build on the current standard of care for patients with metastatic cervical cancer?

The first [data from a] pivotal trial in recurrent or metastatic cervical cancer [were published] in 2009 in the Journal of Clinical Oncology by GOG [investigators], and it was called Protocol 204.3 That study showed that the best cytotoxic chemotherapy doublet was cisplatin and paclitaxel; that changed the world. It continues to be the global standard of the chemotherapy backbone.

In 2015, the Japan Clinical Oncology Group published [results of] a noninferiority trial in the Journal of Clinical Oncology that [showed] we could use carboplatin rather than cisplatin and that paclitaxel could be delivered safely and effectively at 175 mg/m².4

The second concept [investigators pursued] was the addition of an angiogenic, which we all know as bevacizumab. In 2014, that [agent] became the first targeted therapy [available for patients...]

**TABLE.** Efficacy Results in the KEYNOTE-826 Trial 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All-comers</th>
<th>PD-L1 CPS ≥ 1</th>
<th>PD-L1 CPS ≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 308)</td>
<td>(n = 273)</td>
<td>(n = 275)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>24.4 (19.2-NR)</td>
<td>16.5 (14.5-19.4)</td>
<td>16.3 (14.5-19.4)</td>
</tr>
<tr>
<td>HR, 0.67; 95% CI, 0.54-0.84; P &lt; .001</td>
<td>50.4% (43.8%-56.6%)</td>
<td>40.4% (34.0%-46.6%)</td>
<td>53.0% (46.0%-59.4%)</td>
</tr>
<tr>
<td>24-month OS rate (95% CI)</td>
<td>10.4 (9.1-12.1)</td>
<td>8.2 (6.4-8.4)</td>
<td>10.4 (9.7-12.3)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>10.4 (9.1-12.1)</td>
<td>8.2 (6.4-8.4)</td>
<td>10.4 (9.7-12.3)</td>
</tr>
<tr>
<td>HR, 0.65; 95% CI, 0.53-0.79; P &lt; .001</td>
<td>44.7% (38.8%-50.4%)</td>
<td>33.5% (28.0%-39.1%)</td>
<td>45.5% (39.2%-51.5%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>65.9% (60.3%-71.2%)</td>
<td>50.8% (45.1%-56.5%)</td>
<td>68.1% (62.2%-73.6%)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>44.5%</td>
<td>37.9%</td>
<td>45.4%</td>
</tr>
<tr>
<td>PR</td>
<td>21.4%</td>
<td>12.9%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Median DOR (range)</td>
<td>18.0 (1.3-24.2)</td>
<td>10.4 (1.5-22.0)</td>
<td>18.0 (1.3-24.2)</td>
</tr>
</tbody>
</table>

CPS, combined positive score; CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

*Reported ranges are ongoing responses.
with platinum-resistant recurrent gynecologic cancer, and it was added to the platinum/taxane chemotherapy backbone and approved [for use] all over the world. [The regimen] transformed the standard of care from chemotherapy alone to chemotherapy plus bevacizumab in the appropriate patient; there are some contraindications. Approximately 60% of patients [with metastatic cervical cancer] get bevacizumab added to their chemotherapy.

We have evolved the treatment paradigm again with KEYNOTE-826, which added pembrolizumab [to] chemotherapy with or without bevacizumab in the first-line setting. At the first interim analysis of this study, which enrolled 617 patients, it [nearly] met all the therapeutic end points. [There] wasn’t underperformance of the control arm. The control arm had a response rate of 50.8%; however, when pembrolizumab was added, the response rate increased to 66%.1

What really matters is tumor control, and the HR for PFS was 0.65. No new safety signals [were observed], and patient-reported outcomes look as if they’re better [with the addition of pembrolizumab]. Patients are experiencing more tumor shrinkage, longer tumor control, living longer, and they’re feeling better—that transforms the standard of care in a meaningful way.

At 2 years, half of the patients [in the investigatory arm (50.4%)] were still alive, which means half will live longer. We changed the standard of care. I’m so happy to see these [data] for patients because that’s why we do [what we do].

**What is the role of biomarkers in informing treatment with pembrolizumab?**

The accelerated approval of pembrolizumab in the second-line [setting] was restricted to PD-L1-positive patients with a CPS greater than 1.5 Interestingly, [data from] KEYNOTE-826 was positive in all-comers and the reason [for that] is because 89% of the patients were PD-L1 positive. There’s no question that PD-L1 positivity is important, and we should check it to help inform [treatment] decisions. However, if [a patient is not PD-L1 positive], you should still use pembrolizumab.

Eleven percent of patients were PD-L1 negative, and I presume most of [them had] adenocarcinomas. I suspect that many of those [patients] also have a high mutational burden or are mismatch-repair deficient; [these are subsets in which] there is an opportunity for pembrolizumab. Biomarkers are important, but we need better biomarkers moving forward.

**Where will future research directions be focused?**

With the resurgence of checkpoint inhibitors, the first question [that arises is in regard to] sequencing, [such as] should we use checkpoint inhibitors in second-line [treatment]? Remember, [we saw that] cemiplimab-rwlc [Libtayo] is better than physician’s choice of chemotherapy [per data from the phase 3] EMPOWER-Cervical 1 trial [NCT03257267].6 Or should we use all the agents—chemotherapy with or without bevacizumab and pembrolizumab—up front in first line? [Further,] we also have tisotumab vedotin-tftv [Tivdak], an antibody-drug conjugate against tissue factor, which doesn’t need a biomarker because tissue factor is expressed in virtually all cervical cancers.

Finally, it’s all about prevention and screening, and like COVID-19 it’s all about vaccination. The prevention of cervical cancer is about [administering] a vaccine [human papillomavirus (HPV)] quadrivalent (types 6, 11, 16, 18) recombinant vaccine [Gardasil]], which...has been licensed since 2006; it’s broadly reimbursed, and incidentally, it’s made by [Merck], the same company as pembrolizumab.6

The other evolution is that all these cancers are caused by HPV and we have evolved the Papanicolaou test to test for the virus on the cervix. Just like with COVID-19, you see [whether a patient] has the virus, and if they don’t [then] they’re good. We can do that in a patient’s cervix, and it’s now recommended as the primary screening technique [in patients] over the age of 25 years. Patients [should] have [this testing] as their primary modality of seeing whether they are at risk. Every patient [should] protect [themselves].

[Other investigative efforts are now examining the addition of] checkpoint inhibitors, such as pembrolizumab, to chemotherapy and radiation, [such as the] phase 3 study called KEYNOTE-818 [NCT04221945]. Hopefully, [with this approach, we will] cure more patients, which is really what we’re trying to do. I like helping [patients] live longer and I like helping them feel better, but really the goal is to cure patients.

**Is there anything else you would like to add?**

All innovation to help patients is dependent on clinical trials. Clinical trials need 4 components: a patient, an investigator, a sponsor, and a network, which we have through the GOG. Then they need an institution [or] a framework.

All of us need to work together to take our patients and investigators and the trials that we have and teach our institutions, our hospitals, and universities [how to implement them]. If we don’t have clinical trials in our clinics, we cannot help patients. It is only through clinical trials that good things happen.

**REFERENCES**


ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status1-4

**Indication**

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

**Important Safety Information**

**Myelodysplastic syndrome/acute myeloid leukemia** (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1,785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

**Hematologic adverse reactions** (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

**Hypertension and hypertensive crisis** have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

**Posterior reversible encephalopathy syndrome (PRES)** occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

**Embryo-fetal toxicity and lactation**: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.
YOU RESPOND
WITH ZEJULA

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS\(^1,2\)

**OVERALL POPULATION**
(N=733)

- 38% Reduction in the risk of progression or death
- MEDIAN PFS: 13.8 MONTHS WITH ZEJULA
  VS 8.2 MONTHS WITH PLACEBO
  (HR, 0.62; 95% CI, 0.50-0.76) P<0.0001

**HRd POPULATION**
(n=373)

- 57% Reduction in the risk of progression or death
- MEDIAN PFS: 21.9 MONTHS WITH ZEJULA
  VS 10.4 MONTHS WITH PLACEBO
  (HR, 0.43; 95% CI, 0.31-0.59) P<0.0001

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

Important Safety Information (continued)

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

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

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

Please see Brief Summary on the following pages.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

ZEJULA (niraparib) capsules, for oral use

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

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a complete or partial response to first-line platinum-based chemotherapy.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

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

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

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

- a deleterious or suspected deleterious BRCA mutation, or
- germline BRCA mutation and who have progressed more than 6 months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

Select patients for therapy based on a FDA-approved companion diagnostic for ZEJULA.

2 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

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

The duration of therapy with ZEJULA in patients who developed secondary MDS/AML-related AML varied from 0.5 months to 4.5 years. All these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

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

In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 23%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

In NOVA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 1%, and 2%, respectively, of patients. In QUADRRA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 27%, and 12%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients.

Do not start ZEJULA until patients have recovered from hematologic toxicity caused by previous chemotherapy (Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time if hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics [see Dosage and Administration (2.4) and Nonclinical Pharmacology (14.2)].

5.3 Hypertension and Cardiovascular Effects

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

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

In NOVA, Grade 3 or 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 594 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRRA, Grade 3 or 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the dose of ZEJULA, if necessary [see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information].

6 ADVERSE REACTIONS

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

- Myelodysplastic Syndrome/Acute Myeloid Leukemia
- Myelosuppression
- Hypertension
- Hypertensive crisis
- Vascular disorders
- Thrombocytopenia
- Neutropenia
- Anemia
- Professional disorders
- Delirium
- Psychotic disorders
- Hypertension
- Cardiac disorders
- Cardiac arrest
- Cardiovascular effect
- Blood and lymphatic system disorders
- Neutropenia
- Anemia
- Gastrointestinal disorders
- Fatigue
- Nausea
- Constipation
- Vomiting
- General disorders and administration site conditions
- Acute kidney injury
- Respiratory, thoracic and mediastinal disorders
- Cough
- Vascular disorders

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

The most common adverse reactions of all grades in >10% of 1,314 patients who received ZEJULA in the pooled PRIMA, NOVA, and QUADRRA trials were nausea (65%), thrombocytopenia (65%), anemia (58%), vomiting (47%), decreased appetite (39%), weight loss (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspepsia (22%), rash (21%), diarrhea (21%), hypertension (17%), cough (10%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.3 to 29 months).

All Patients Receiving ZEJULA in PRIMA

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

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.5%), and nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

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

Table 1: Adverse Reactions Reported in ≥1% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>ZEJULA (n=367)</td>
<td>Placebo (n=179)</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia b</td>
<td>28 11 5 0</td>
<td>29 8 1 0.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>64 18 31 2</td>
<td></td>
</tr>
<tr>
<td>Neutropenia b</td>
<td>30 6 20 2</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57 28 1 1</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>49 20 1 0.4</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 12 1 1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>ZEJULA (n=367)</td>
<td>Placebo (n=179)</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia b</td>
<td>28 11 5 0</td>
<td>29 8 1 0.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66 5 39 0.4</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>64 18 31 2</td>
<td></td>
</tr>
<tr>
<td>Neutropenia b</td>
<td>30 6 20 2</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57 28 1 1</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>49 20 1 0.4</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 12 1 1</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA: Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in ≥2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (5% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=144)</td>
<td>Placebo (n=244)</td>
<td>ZEJULA (n=144)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74%</td>
<td>13%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71%</td>
<td>36%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66%</td>
<td>57%</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51%</td>
<td>29%</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46%</td>
<td>21%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40%</td>
<td>23%</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36%</td>
<td>34%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35%</td>
<td>17%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Common Terminology Criteria for Adverse Events version 4.02.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=179)</td>
<td>Placebo (n=367)</td>
<td>ZEJULA (n=179)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54%</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>50%</td>
<td>28%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36%</td>
<td>8%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28%</td>
<td>11%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53%</td>
<td>21%</td>
</tr>
<tr>
<td>Constipation</td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48%</td>
<td>36%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>48%</td>
<td>5%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=180)</td>
<td>Placebo (n=368)</td>
<td>ZEJULA (n=180)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81%</td>
<td>70%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>70%</td>
<td>36%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>63%</td>
<td>15%</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>63%</td>
<td>56%</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>60%</td>
<td>27%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52%</td>
<td>30%</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43%</td>
<td>17%</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44%</td>
<td>30%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41%</td>
<td>22%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31</td>
<td>19%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28</td>
<td>15%</td>
</tr>
</tbody>
</table>

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=86)</td>
<td>Placebo (n=179)</td>
<td>ZEJULA (n=86)</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85%</td>
<td>56%</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72%</td>
<td>21%</td>
</tr>
<tr>
<td>Decrease in white blood cell count</td>
<td>66%</td>
<td>37%</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>53%</td>
<td>25%</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase</td>
<td>36%</td>
<td>23%</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase</td>
<td>28%</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=367)</td>
<td>Placebo (n=179)</td>
<td>ZEJULA (n=367)</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85%</td>
<td>56%</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72%</td>
<td>21%</td>
</tr>
<tr>
<td>Decrease in white blood cell count</td>
<td>66%</td>
<td>37%</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>53%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.
Table 7. Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4* (n=463) %</th>
<th>Grades 3-4* (n=463) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>51.27</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52.28</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20.13</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67.10</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>44.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>170.2</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56.7</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27.2</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>29.3</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19.04</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22.3</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.5</td>
<td></td>
</tr>
</tbody>
</table>

*Common Terminology Criteria for Adverse Events version 4.02.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ZEJULA. Because these reactions are reported voluntarily from a population of uncertain size, it is always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Blood and Lymphatic System Disorders:**
- Anemia
- Neutropenia

**Gastrointestinal Disorders:**
- Nausea
- Vomiting
- Constipation
- Abdominal pain
- Diarrhea

**General Disorders and Administration Site Conditions:**
- Fatigue

**Infections and Infestations:**
- Urinary tract infection

**Investigations:**
- Blood alkaline phosphatase increased
- AST/ALT elevation

**Metabolism and Nutrition Disorders:**
- Decreased appetite

**Musculoskeletal and Connective Tissue Disorders:**
- Musculoskeletal pain

**Nervous System Disorders:**
- Headache
- Dizziness

**Psychiatric Disorders:**
- Insomnia

**Respiratory, Thoracic and Mediastinal Disorders:**
- Dyspnea
- Cough

**Vascular Disorders:**
- Hypertension

**Vascular Disorders:**
- Hypertension

**Renal and Urinary Disorders:**
- Acute kidney injury

**Other Adverse Reactions:**
- Cough, vomiting, nausea, diarrhea, fatigue, infections, and other adverse reactions have been reported during postmarketing use of ZEJULA.

**Laboratory Findings:**

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4* (n=463) %</th>
<th>Grades 3-4* (n=463) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83.26</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66.5</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60.28</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57.18</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53.9</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46.1</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40.4</td>
<td></td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40.8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36.04</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34.15</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>Increased albumin</td>
<td>27.2</td>
<td></td>
</tr>
</tbody>
</table>

**General Laboratory Findings:**

- The following laboratory findings have been reported with ZEJULA:
  - Decreased hemoglobin
  - Increased alkaline phosphatase
  - Increased gamma glutamyl transferase
  - Increased creatinine
  - Decreased sodium
  - Decreased neutrophils
  - Increased alkaline phosphatase
  - Increased albumin

**Other Laboratory Findings:**

- Changes in laboratory findings have been observed with ZEJULA.

**Dosage and Administration:**

- ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. In patients who also have aspirin hypersensitivity, use ZEJULA with caution.

**Use in Specific Populations:**

- **Pregnancy:**
  - ZEJULA can cause fetal harm when administered to a pregnant woman. **[See Warnings and Precautions (5.6).]**

- **Breastfeeding:**
  - ZEJULA is excreted in human milk. **[See Nonclinical Toxicology (13.1) of full prescribing information].**

- **Pediatric Use:**
  - The safety and effectiveness of ZEJULA have not been established in pediatric patients. **[See Use in Specific Populations (8.1).]**

**Contraindications:**

- Patients with known hypersensitivity to niraparib or any component of ZEJULA should not take ZEJULA. **[See Warnings and Precautions (5.4) and Use in Specific Populations (8.1).]**

**Warnings and Precautions:**

- **Hematologic Toxicity:**
  - ZEJULA can cause hematologic toxicity. **[See Clinical Pharmacology (13.3) of full prescribing information].**

- **Gastrointestinal Toxicity:**
  - ZEJULA can cause gastrointestinal toxicity. **[See Clinical Pharmacology (13.3) of full prescribing information].**

- **Neurologic Toxicity:**
  - ZEJULA can cause neurologic toxicity. **[See Clinical Pharmacology (13.3) of full prescribing information].**

- **Respiratory Toxicity:**
  - ZEJULA can cause respiratory toxicity. **[See Clinical Pharmacology (13.3) of full prescribing information].**

- **Vascular Toxicity:**
  - ZEJULA can cause vascular toxicity. **[See Clinical Pharmacology (13.3) of full prescribing information].**

**Adverse Reactions:**

- The following adverse reactions have been observed with ZEJULA:
  - Anemia
  - Neutropenia
  - Gastrointestinal disturbances
  - Cough
  - Dyspnea
  - Respiratory, thoracic, and mediastinal disorders
  - Acute kidney injury
  - Renal and urinary disorders
  - Dizziness
  - Nervous system disorders
  - Decreased appetite
  - Metabolism and nutrition disorders
  - AST/ALT elevation
  - Decreased sodium
  - Decreased leukocytes
  - Decreased hemoglobin
  - Increased alkaline phosphatase
  - Posterior reversible encephalopathy syndrome
  - Hypersensitivity (including anaphylaxis)
  - Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).
  - Respiratory, allergic, and gastrointestinal disorders: Non-infectious pneumonitis.
  - Skin and subcutaneous tissue disorders: Phototoxicity.
Practice Recommendations Make Room for Telemedicine in Oncology Care

by BRITTANY LOVELY

TELEMEDICINE SOLIDIFIED ITS ROLE as a new standard in patient care during the COVID-19 pandemic. The American Society of Clinical Oncology (ASCO) has issued standards and guidance pertaining to its use for patients receiving oncology-specific care and to the roles of various providers who may interact with patients over their course of treatment.

Though not a novel concept, telemedicine in medical practice has struggled to see widespread use in practices. Pivoting to meet the demands of maintaining uninterrupted, ongoing care while in-person visits were restricted, organizations including ASCO issued interim policies and guidelines at the academic and community practice level. ASCO adopts the language defined in the New England Journal of Medicine Catalyst to refer to telemedicine as that which "encompasses the use of technologies and telecommunication systems to administer health care to patients who are geographically separated from providers."

A multidisciplinary panel of expert health care providers, a patient representative, and a health research methodologist contributed to the creation and review of the ASCO Standards and Practice Recommendations on telemedicine in oncology. The participants conducted a systematic review of the available literature concerning different methods of telehealth delivery in oncology as well as oncology-specific standards previously issued on related topics.

FOR WHICH PATIENTS IS TELEMEDICINE CARE APPROPRIATE?

Investigators determined the specific patient populations for whom telemedicine may be an appropriate option when in-person visits are not possible. They considered whether outcomes for patients differed between those who received in-person care vs those who had telemedicine visits. Several categories were identified as appropriate for standard or long-term treatment telemedicine visits (FIGURE 1).

In-person visits preferred by the care provider included those for initial consultations, initial delivery of antineoplastic treatments, and delivery of key information regarding a patient’s treatment plan. For example, an in-person visit would be better for relaying the complex cancer treatment needs and information concerning disease progression; it would also be more suitable for physical examinations required during follow-up visits. However, the investigators noted that telemedicine may be used if local care providers are able to perform physical examinations and consult with the primary treatment team via referral communication.

The physician-patient relationship, specifically concerning initial meetings with the care team, should include an in-person visit at the primary care location. Follow-up visits and other responsibilities consistent with community standards should mandatorily be executed via telemedicine following the initial visit. As pandemic-related policies ease, the expansion of services covered as telemedicine services by the Centers for Medicare & Medicaid Services (CMS) has already been implemented when CMS permanently expanded coverage in December 2020.

The 2022 proposal for coverage looks to maintain this expanded coverage through December 21, 2023, to provide evidence for the review of services that should be permanently added to the coverage.

ONCOLOGY-SPECIFIC WORKFLOW IMPLEMENTATION CONSIDERATIONS

Safety and quality of care are the foremost concerns in the adoption of telemedicine services. Objective monitoring and timely reporting of patient outcomes, physical examinations, and laboratory tests, are essential to providing the highest quality of continued care. Data including rates of emergency department visits, adverse effects, and hospitalizations are also vital.

The ASCO standards highlight that those operating procedures for interventions that are delivered asynchronously (ie, patient symptom reporting) should outline appropriate and timely responses to patient-reported outcomes.

For example, adequate documentation for each telemedicine visit should confirm the patient’s agreement to partake in a telemedicine visit, the date of the visit, location of the visit for both patient and provider, participants, and what technology was used (ie, audio only, videoconferencing, etc).

Although technology certification is not required, both patients and providers should receive orientation on the platform and instructions should be delivered to the patient if the provider needs to assess an area of the body. The authors note that a technology support individual should be present for clinical visits to troubleshooting any issues.

Additionally, to enhance the efficiency of telemedicine as it relates to patient...
adherence to prescribed treatments, practices should implement automated reminders tailored to the individual patient. These reminders should consider the health and technological literacy.

Recommended steps for practices for sustaining telemedicine oncology program are outlined in FIGURE 2.1

Following a review of the clinical practice guidelines for teleoncology issued by the Clinical Oncology Society of Australia, ASCO’s expert panel endorsed the recommendations pertaining to the role of allied health professionals in telehealth interventions. Specifically, telephone-based evaluations can help to facilitate changed behaviors, improved function, and improved psychologic or psychosocial status; computerized screening or assessment may be used to collect information on patient status and assist with referral to allied health oncology services; hybrid telehealth systems may be used as alternative models of care; and videoconferencing may be used to deliver health assessments and treatment services from allied health professionals to oncology patients.1,7

For more detailed information on process, the expert panel endorses the American Medical Association’s Telehealth Implementation Playbook, which outlines the process of making telemedicine an integral part of a practice from identifying a need through evaluating success.8

LIMITS OF TELEMEDICINE

In addition to its potential to expand access for many patients, telemedicine’s limitations are also addressed in the standards. Care via telemedicine consultations has been determined as being appropriate for some populations; however, the investigators noted that patients with hearing loss, vision loss, or cognitive limitations who have no alternative support systems to assist them with telemedicine visits should continue with in-person visits.1

Additionally, patients without access to technology (ie, broadband internet or devices to host the visit) and those with limited health literacy should also seek in-person care. “Within many studies, telehealth is cited as a way of reducing costs for patients by eliminating travel and associated fuel and lodging charges and minimizing the time away from paid work,” the authors of the ASCO standards wrote in the discussion. “However, for patients who do not have access to sufficient broadband to participate in a videoconference or do not have a mobile phone, inequity of access will continue and may be exacerbated.”

The authors noted that, “when possible, patients may be given the option of in-person or telemedicine visits, according to personal preference.”1

FUTURE APPLICATIONS IN CLINICAL TRIALS

To increase recruitment for clinical trials, the ASCO standards recommend that virtual participation be offered, where feasible, as it reduces the burden of trial participation on patients.1

“Many clinical practice guidelines, including those produced by ASCO, call for inclusion of patients in clinical trials whenever possible,” the authors wrote. “However, many patients, such as those who live outside of urban centers, face barriers to access, and fewer than 10% of patients with cancer in the United States are enrolled in clinical trials.”
The rise in use of telehealth services during the COVID-19 pandemic has left many patients and primary care providers (PCPs) wondering whether adaptations in care will continue expanding in the months and years to come. According to Meg Barron, vice president of digital health strategy at the American Medical Association (AMA), the percentage of PCPs offering telehealth services doubled from 14% to 28% between 2016 and 2019, well before the COVID-19 pandemic. Barron estimates that 60% to 90% of PCPs have integrated a broader array of telehealth services into their practice. Of those, Barron said approximately half are using telehealth services for the first time.

A large portion of PCPs have witnessed first-hand the benefits that expanding their digital services and tools can provide in ensuring that safe and efficient care is delivered to their patients. However, many PCPs have questions regarding how the integration and growth of telehealth services will continue beyond the pandemic.

A report from McKinsey cites that 40% to 90% of PCPs were offering virtual care; however, just over half (57%) of PCPs said that they would prefer virtual care over in-person visits. Should pandemic era changes prove to be lasting, efforts will be needed. These include better integration of virtual health-related activities into daily workflows for PCPs and improvements to care models to incorporate remote monitoring and at-home care.

Changes for payers will also affect the continuum of virtual care. For example, adjustments to commercial insurance reimbursement and the ability to treat and prescribe medication for patients across state lines may bridge disparities in care and be a meaningful step forward in health equity.

The recommendations from ASCO include using virtual services for initial discussions of trial information as well as assessment of eligibility; remote monitoring of symptoms and adverse effects; remote initiation of treatment conducted through sponsors or contract research organizations; shipping oral anticancer agents directly to patients when applicable with a follow-up call to review dosage schedules; permitting local laboratory testing for blood and biopsy samples; reviewing the necessity of testing frequency in trial protocols; and increasing the use of patient-reported outcomes as study end points.1

“Changes [implemented during the COVID-19 pandemic] may have a lasting impact on clinical trials and result in improved access and participation over the long term for remote or less-mobile patients,” the authors wrote.

REFERENCES

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OPDIVO® + YERVOY®

For PD-L1 ≥1% mNSCLC patients, across histology without EGFR or ALK mutations

OPDIVO, in combination with YERVOY, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 ≥1% as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

Primary analysis (PD-L1 ≥1%): median OS was 17.1 months (95% CI: 15.0–20.1) with OPDIVO + YERVOY vs 14.9 months (95% CI: 12.7–16.7) with chemo (HR=0.79; 95% CI: 0.67–0.94; P=0.0066).1

OPDIVO + YERVOY with limited chemo

For r/m NSCLC patients, regardless of PD-L1 expression and histology

OPDIVO, in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

Primary analysis: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY and chemo vs 10.7 months (95% CI: 9.5–12.5) with chemo (HR=0.69; 95% CI: 0.55–0.87; P=0.0006).1

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

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

*Vs chemo. In Checkmate 227, patients received platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin; SQ: gemcitabine + carboplatin or cisplatin.

† In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin.1,5

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

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

Severe and Fatal Immune-Mediated Adverse Reactions

● Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
**OPDIVO + YERVOY Efficacy: OS**

**Checkmate 227:** In a cross-histology trial for patients with mNSCLC (PD-L1 ≥1%)  
**Durable survival with OPDIVO + YERVOY: 29% of patients alive at 4 years**

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

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPDIVO + YERVOY</td>
</tr>
<tr>
<td>6</td>
<td>295</td>
</tr>
<tr>
<td>12</td>
<td>244</td>
</tr>
<tr>
<td>18</td>
<td>190</td>
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<tr>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>4 YEARS</td>
<td></td>
</tr>
</tbody>
</table>

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

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

- ORR: 36% (144/396, 95% CI: 32–41), CR=5.8%, with OPDIVO + YERVOY and 30% (120/397, 95% CI: 26–35), CR=1.8%, with chemo
- mDOR was 23.2 months (95% CI: 15.5–33.9) with OPDIVO + YERVOY in the extended follow-up analysis
- mDOR was 6.7 months (95% CI: 5.6–7.6) with chemo in the extended follow-up analysis
- Median follow-up of 54.8 months

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**
- In Checkmate 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + carboplatin or cisplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + carboplatin or cisplatin.
- In Checkmate 227 Part 1a, PFS, ORR, and DOR were pre-specified descriptive analyses. The primary efficacy outcome measure was OS.
- mDOR was 23.2 months (95% CI: 15.5–33.9) with OPDIVO + YERVOY in the extended follow-up analysis
- mDOR was 6.7 months (95% CI: 5.6–7.6) with chemo in the extended follow-up analysis
- Median follow-up of 54.8 months

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

Please see additional Important Safety Information for OPDIVO and YERVOY throughout and accompanying brief summary of US Full Prescribing Information for OPDIVO and YERVOY on the following pages.
**OPDIVO + YERVOY with limited chemo Efficacy: OS**

**Checkmate 9LA**: For r/m NSCLC patients, regardless of PD-L1 expression and histology

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

Overall survival (ITT)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>OPDIVO + YERVOY + chemo</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>326</td>
<td>319</td>
</tr>
<tr>
<td>3</td>
<td>292</td>
<td>260</td>
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<tr>
<td>6</td>
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<td>8</td>
</tr>
<tr>
<td>36</td>
<td>102</td>
<td>0</td>
</tr>
</tbody>
</table>

Minimum follow-up of 24.4 months.

- Efficacy results from the pre-specified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) with an 8.1-month minimum follow-up.

- Median PFS at the 23.3-month minimum follow-up: 6.7 months (95% CI: 5.6–7.8) with OPDIVO + YERVOY with chemo and 5.3 months (95% CI: 4.4–5.6) with chemo alone; HR=0.67 (95% CI: 0.56–0.79).

- ORR at the 6.5-month minimum follow-up: 38% (95% CI: 33–43) with OPDIVO + YERVOY with chemo and 25% (95% CI: 21–30) with chemo.

- Median OS at the 24.4-month follow-up analysis: 15.8 months (95% CI: 13.9–19.7) with OPDIVO + YERVOY with chemo and 11.0 months (95% CI: 9.5–12.7) with chemo; HR=0.72 (95% CI: 0.61–0.86).

- 32% of patients enrolled had SQ disease; 68% had NSQ disease.

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

*Two cycles of platinum-doublet chemo.

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

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

**SELECT IMPORTANT SAFETY INFORMATION**

**Serious Adverse Reactions**

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

**Common Adverse Reactions**

- In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%).
**OPDIVO + YERVOY with limited chemo Efficacy: OS**

**Checkmate 9LA:** For r/m NSCLC patients, regardless of PD-L1 expression and histology

**Consistent OS benefit across PD-L1 expression at 2 years**

**OPDIVO + YERVOY with limited chemo**

**Extended follow-up analysis**

**Initial pre-specified interim analysis (minimum follow-up 8.1 months)**

- **OPDIVO + YERVOY + chemo (n=135)**: 14.0 mos (95% CI: 13.2–NR)  
  HR=0.65 (95% CI: 0.46–0.92)

- **Chemo (n=129)**: 10.0 mos (95% CI: 7.7–13.7)  
  HR=0.70 (95% CI: 0.56–0.89)

**Minimum follow-up of 24.4 months**

- **HR=0.67 (95% CI: 0.51–0.88)**

**Minimum follow-up of 24.4 months**

- **HR=0.70 (95% CI: 0.56–0.89)**

**Number at risk**

- **OPDIVO + YERVOY + chemo**: 135, 120, 107, 90, 85, 73, 66, 55, 50, 31, 13, 6, 2, 0  
  Time (months): 2, 3, 6, 12, 15, 18, 21, 27, 33, 36, 39

- **Chemo**: 129, 116, 90, 68, 58, 47, 37, 32, 27, 21, 7, 2, 0, 0  
  Time (months): 2, 3, 6, 12, 15, 18, 21, 27, 33, 36, 39

**Limitation:** Checkmate 9LA was not powered to detect differences in the treatment effect in PD-L1 subgroups; therefore, results from this exploratory analysis should be interpreted with caution because of the limited patient numbers and potential imbalances in baseline characteristics within the subgroup.

- Primary analysis in the ITT population at the 8.1-month minimum follow-up: median OS was 14.1 months (95% CI: 13.2–16.2) with OPDIVO + YERVOY vs 10.7 months (95% CI: 9.5–12.5) with chemo alone; HR=0.69 (95% CI: 0.55–0.87); P=0.006**8**

- At the 24.4-month minimum follow-up, median OS for PD-L1 <1% was 17.7 months (95% CI: 13.7–20.3) with OPDIVO + YERVOY with limited chemo and 9.8 months (95% CI: 7.7–13.5) with chemo; HR=0.67 (95% CI: 0.51–0.88)**9**

- At the 24.4-month minimum follow-up, median OS for PD-L1 ≥1% was 15.8 months (95% CI: 13.2–22.2) with OPDIVO + YERVOY with limited chemo and 10.9 months (95% CI: 9.5–13.2) with chemo; HR=0.70 (95% CI: 0.56–0.89)**9**

*Two cycles of platinum-doublet chemo.

**SELECT IMPORTANT SAFETY INFORMATION**

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

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY.

  Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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

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

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

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

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

Please see updated NCCN Guidelines® for a complete listing of all NCCN-recommended agents, including preferred options. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

**SELECT IMPORTANT SAFETY INFORMATION**

Severe and Fatal Immune-Mediated Adverse Reactions

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

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

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

Please visit the website for more information.
SELECT IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

- ODPIVO and YERVOY can cause immune-mediated nephritis.
- ODPIVO and YERVOY can cause immune-mediated dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.
- Withhold or permanently discontinue ODPIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

**Other Immune-Mediated Adverse Reactions**

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

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

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

**Infusion-Related Reactions**

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

**Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with ODPIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between ODPIVO or YERVOY and allogeneic HSCT.

- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with ODPIVO and YERVOY prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

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

**Increased Mortality in Patients with Multiple Myeloma when ODPIVO is Added to a Thalidomide Analogue and Dexamethasone**

- In randomized clinical trials in patients with multiple myeloma, the addition of ODPIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Lactation**

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

**Serious Adverse Reactions**

- In Checkmate 227, serious adverse reactions occurred in 58% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea, colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 1.4% of patients (n=358). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemorhysis in the setting of thrombocytopenia.

**Common Adverse Reactions**

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

Please see additional Important Safety Information for ODPIVO and YERVOY throughout and accompanying brief summary of US Full Prescribing Information for ODPIVO and YERVOY on the following pages.
OPDIVO (nivolumab), in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC), whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test (see Dosage and Administration, with no ESR or ALK genomic tumor aberrations.

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

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be indicative of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, appropriate work-up should be performed, including infectious, inflammatory, metabolic, neurological, and other conditions known to cause similar signs or symptoms.

The most common (incidence ≥25%) severe (incidence ≥5%) immune-mediated adverse reactions of any organ system or tissue for OPDIVO in combination with ipilimumab, in patients without unresectable brain metastases, are listed in the table below. Immune-mediated adverse reactions can occur within weeks of the initiation of therapy.

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<thead>
<tr>
<th>Immune-Mediated Adverse Reaction</th>
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### Table 2: Laboratory Values Worsening from Baseline (mean >20% of Patients on OPDIVO (nivolumab) and ipilimumab - CHECKMATE-227)

<table>
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<th>Laboratory Abnormality</th>
<th>OPDIVO and ipilimumb</th>
<th>Platinum-doublet Chemotherapy</th>
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<tbody>
<tr>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>46</td>
<td>3.6</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>46</td>
<td>5</td>
</tr>
</tbody>
</table>

### Chemistry

- **Hyperkalemia**: 41, 12, 26, 4.9
- **Increased AST**: 39, 5, 26, 0.4
- **Increased ALT**: 36, 7, 27, 0.7
- **Increased bilirubin**: 35, 1.4, 14, 3.5
- **Increased amylase**: 34, 3.8, 20, 0.2
- **Hypocalcemia**: 28, 17, 18, 1.9
- **Hypokalemia**: 28, 3.7, 17, 1.3
- **Increased creatinine**: 27, 4.4, 19, 0.5

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO (491 to 335 patients) and ipilimumab (491 to 335 patients).

### Table 3: Adverse Reactions in >5% of Patients Receiving OPDIVO and ipilimumb and Platinum-Doublet Chemotherapy - CHECKMATE-816

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPDIVO and ipilimumb (n=865)</th>
<th>Platinum-doublet Chemotherapy (n=471)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Fatiguea</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>General</td>
<td>14</td>
<td>0.6</td>
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</table>

### Table 4: Laboratory Values Worsening from Baseline (mean >20% of Patients on OPDIVO (nivolumab) and ipilimumb - CHECKMATE-227)

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<td>Grades 3-4 (%)</td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>45</td>
<td>7</td>
</tr>
<tr>
<td>Increased AST</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>43</td>
<td>4.8</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>31</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>30</td>
<td>7</td>
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<td>12</td>
</tr>
<tr>
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<td>21</td>
<td>1.7</td>
</tr>
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### Notes

- a Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO (491 to 335 patients) and ipilimumab (491 to 335 patients).
- c Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, and decreased free tri-iodothyronine.
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.
Table 3: Adverse Reactions in >10% of Patients Receiving YERVOY (ipilimumab) and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>YERVOY and Nivolumab (n=358)</th>
<th>Platinum-Doublet Chemotherapy (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>10.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Decreased</td>
<td>11.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased</td>
<td>11.6</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Table 4: Laboratory Values Worsening from Baseline Occurring in >20% of Patients on YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

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<tr>
<td>Hematology</td>
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<tr>
<td>Anemia</td>
<td>20.0</td>
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<td>Leukopenia</td>
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<td>10.0</td>
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<tr>
<td>Thrombocytopenia</td>
<td>23.0</td>
<td>4.3</td>
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<tr>
<td>Chemistry</td>
<td></td>
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<tr>
<td>Hypokalemia</td>
<td>45.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>37.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>34.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>31.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>31.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>30.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>30.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>29.0</td>
<td>1.2</td>
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<tr>
<td>Hypothermia</td>
<td>26.0</td>
<td>1.4</td>
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Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. YERVOY and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Immuno-Genetics

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

Of 481 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part I, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, 491 patients evaluable for anti-nivolumab antibodies 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 6% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of interactions to YERVOY in patients with anti-ipilimumab antibodies. Of 358 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2% had neutralizing antibodies against nivolumab.

Postmarketing Experience

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

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

Immune System: Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

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Increased amylase 30 7 19 1.3

Increased alkaline phosphatase 31 1.2 26 0.3

Increased lipase 31 12 10 2.2

Increased alanine aminotransferase 30 7.0 19.0 13.0

Increased aspartate aminotransferase 30 3.5 22.0 0.3

Increased gamma-glutamyltransferase 29.0 1.2 33.0 0.6

Increased lactate dehydrogenase 26.0 1.4 22.0 1.8

Increased creatinine 26.0 1.2 23.0 0.6

Increased bilirubin 25.0 1.2 3.0 0.3

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UAMS Winthrop P. Rockefeller Cancer Institute Pushes Liquid Biopsy Research Forward

by DONALD J. JOHANN JR, MD, MSC

THE USE OF A ROUTINE blood test to assess and monitor patients with cancer, especially in a longitudinal manner, has long been the holy grail of cancer research. At the University of Arkansas for Medical Sciences (UAMS) Winthrop P. Rockefeller Cancer Institute, we have made big steps toward achieving that goal in the past 5 years.

With the analysis of a simple blood test, also known as a liquid biopsy, we can find circulating tumor DNA (ctDNA), which are nucleic acid biomolecules shed by a tumor into the blood and detected by next-generation sequencing (NGS). Some of these tests are commercially available and approved by the FDA for patients with advanced or metastatic disease. Investigators at UAMS are now working to translate foundational work into cutting-edge care for patients with cancer at all stages of disease and across tumor types and eventually for screening assays.

These investigative efforts have been made possible by recent advancements in molecular biology, scientific instrumentation including sequencing technology, computational science, and platforms that are able to manage massive amounts of data. The vision is to combine the power of these approaches with clinical knowledge to advance outcomes for patients with cancer, especially in a longitudinal manner, and improve methods of drug development.

UAMS is conducting a clinical trial (NCT02597738), which is funded by the FDA, to develop an advanced liquid biopsy method for diagnosing and monitoring lung cancer. In a related effort, we have been a key part of an FDA-funded international collaboration whose recently published findings reveal that 5 commercially available assays can reliably detect ctDNA of late-stage and metastatic cancers. The study team who published the findings, in the April issue of *Nature Biotechnology*, includes investigators at the FDA’s National Center for Toxicological Research in Jefferson, Arkansas, and 12 laboratories in Europe, Australia, Asia, and the United States. Springer Nature’s Behind the Paper channel further explores aspects of how this research paper came to be and where subsequent research may lead.

Our team’s work at UAMS is part of the effort led by the FDA to develop standard protocols and quality control measures for NGS in precision medicine so that it can be brought into everyday practice for patients. The aim of the study is to lay the foundation for a transformation in oncology practice, clinical trials protocol, and drug development with the analytical validation of assays based on ctDNA. The ramifications of the liquid biopsy advances from this study were recently profiled in *The Scientist*.

The FDA has provided more than $3.5 million to liquid biopsy studies as part of the 21st Century Cures Act approved by Congress in 2016. This clinical trial for patients with lung cancer provides a glimpse into the near future of personalized cancer treatment (FIGURE). Surgeons at UAMS provide our team with tumor samples and in the laboratory we perform NGS on the tumor and regrow the tumor using different methods. Then the team tests individual existing drugs and novel drug combinations to find the most effective treatment for that patient’s tumor.

The information can then be used to determine the best therapies should a patient’s cancer return. Additionally, information is compiled so investigators can identify patterns and trends regarding which treatments are most efficacious for different types of tumors. Patients in the clinical trial give blood samples at multiple stages (standard-of-care visits) of treatment. The investigative team will begin to measure whether the tests improve outcomes through earlier detection of cancer recurrence by the liquid biopsy longitudinal monitoring.

The collaborative element is very important to this work. UAMS is working with prestigious National Cancer Institute comprehensive cancer centers, including Memorial Sloan Kettering Cancer Center in New York, New York, the University of Southern California in Los Angeles, and other Blood Profiling Atlas in Cancer (BloodPAC) members, to accelerate the development of liquid biopsies for cancer treatment guidance and less invasive clinical care.

The UAMS team has contributed to the following high-impact publications concerning liquid biopsies and NGS approaches for oncology:

- **Clinical Pharmacology & Therapeutics**: addresses how sample collection (blood draws) should be performed (ie, preanalytical variables) for liquid biopsies
- **Clinical Chemistry**: outlines a series of generic
Liquid biopsies are the future of cancer medicine. Compared with traditional tissue biopsy approaches that may require a small operation or an interventional radiology approach, liquid biopsies are safer, faster and less expensive. They also provide a more effective approach toward longitudinal analysis, assessment of minimal residual disease, and decision-making for adjuvant therapy based on a patient’s quantitative data assessing burden of disease from their liquid biopsy assay. In summary, the liquid biopsy provides for more effective molecular diagnostics and improved drug development, and we are on the cusp of making it a more routine reality for our patients.

REFERENCES

FIGURE. Feasibility Study to Further the Development of Lung Cancer–Based Precision Medicine (NCT02597738)
Bring early-stage breast cancer into focus.
TEST for biomarkers, such as BRCA, HR, and HER2, at diagnosis.

ADAPT your treatment approach for curative intent, based on biomarker results.

TakeACloserLookBC.com
THE BREAST CANCER SUSCEPTIBILITY genes BRCA1 and BRCA2 are crucial players in the maintenance of genomic integrity through their role in the homologous recombination pathway of DNA repair. More than 25 years ago, germline BRCA1/2 mutations were first identified as the primary cause of hereditary breast and ovarian cancers and have since been linked to increased risk of many other cancer types.1 2

Prophylactic management strategies have been developed for patients with BRCA1/2 mutations who do not yet have cancer. Because tumors with these variants exhibit enhanced sensitivity to DNA-damaging therapeutics, BRCA1/2 mutations also have important implications for the treatment of patients with cancer.3 4

A novel class of targeted therapies has been developed to exploit this apparent Achilles’ heel. Numerous PARP inhibitors are approved for the treatment of ovarian, breast, pancreatic, and—most recently—prostate cancers that display BRCA1/2 mutations or other defects in the homologous recombination repair (HRR) pathway.4

Currently, BRCA1-mutant and BRCA2-mutant cancers are treated as a single clinical entity, but there is growing appreciation that their distinct cellular roles may create significant differences in the cancers they drive, patient prognosis, and even response to therapy. Clinical data regarding the potential differential sensitivity of BRCA1-mutated and BRCA2-mutated cancers to PARP inhibitor therapy are limited but suggest relatively lower efficacy in patients with BRCA1 mutations.

In prostate cancer, at least, a recent analysis showed this to be a class effect across PARP inhibitors. Moving forward, investigators are working to tease apart the clinical implications of BRCA1 and BRCA2 mutations across cancer types.4–10

IMPLICATIONS OF MUTATIONS

The BRCA1 and BRCA2 genes were first linked to breast and ovarian cancer susceptibility in the mid-1990s,7 with an inherited mutation in a single allele of either gene associated with an increased risk of both types of cancer. These mutations are the predominant cause of hereditary breast and ovarian cancer syndrome, which accounts for approximately 5% to 10% of all breast cancer cases.3

In the general population, women’s lifetime risk of developing breast cancer is 12.5%, although certain ethnic populations exhibit a higher likelihood.3 By contrast, approximately 40% to 70% of women with BRCA1/2 mutations will develop breast cancer by age 70. BRCA1/2 mutations also significantly increase the risk of contralateral breast cancer and increase the risk of breast cancer in men, although the absolute risk for men remains much lower than for women.3

FIGURE. Targeting DNA Repair Pathway16

Compared with breast cancer, BRCA1/2 mutations confer a slightly lower risk of ovarian cancer, with an estimated 40% to 45% of BRCA1 mutation carriers (ie, patients with a germline mutation in 1 allele of the gene) and 10% to 20% of BRCA2 mutation carriers developing ovarian cancer by age 70.11

It remains unclear why BRCA1/2 mutations drive predisposition to breast and ovarian cancers in particular. Several hypotheses have been posited, including an association with the hormonally driven nature of these cancers.1 3 BRCA1/2 mutations also are associated with increased risk of several other cancer types including prostate cancer, another hormonally driven cancer, and pancreatic cancer.

BRCA1/2 mutations have been identified in various other cancer types, but their role in tumorigenesis is less certain. A recent analysis of more than 17,000 patients with 55 types of cancer found that tumor lineage largely determines whether a BRCA1/2 mutation acts as a cancer driver.

The most frequently seen cancers in BRCA1/2 mutation carriers—breast, ovarian, pancreatic, and prostate—were also the most likely to have traits associated with loss of HRR proficiency, such as biallelic BRCA1/2 inactivation. The results suggested that BRCA1/2 alterations may function as passenger mutations in these less common cancer types. Although much rarer, biallelic somatic mutations in the BRCA1/2 genes also have been described in a number of cancer types.12 13

In most cases, when cancer develops in a BRCA1/2 mutation carrier it is the result of biallelic BRCA1/2 inactivation through loss of the remaining wild-type allele (known as loss of heterozygosity [LOH]). This leads to an inability of the cell to perform homologous recombination-based DNA repair, a condition that has been dubbed HRR deficiency (HRD).13 HRD leads to the accumulation of double-strand DNA breaks (DSBs), resulting in genomic instability that drives cancer development.1 14 Cancer can develop in BRCA1/2 mutation carriers via mechanisms other than LOH, and not all of these mechanisms are associated with equivalent levels of HRD.14
Once a patient has developed cancer, BRCA1/2 mutations can also have therapeutic implications because tumors with these mutations are more sensitive to DNA-damaging drugs, such as platinum-based chemotherapy.2,4,5,17 Furthermore, PARP inhibitors have been developed that exploit the HRR defects of BRCA1/2-mutant cells. PARP is an enzyme involved in the repair of single-strand DNA breaks (SSBs). SSBs accumulate in the presence of a PARP inhibitor, leading to DSBs, which must be repaired to prevent cell death. Therefore, tumor cells with HRD, in which DSBs cannot be effectively repaired, are uniquely susceptible to PARP inhibition (FIGURE 1).3

Olaparib (Lynparza) became the first FDA-approved PARP inhibitor in 2014 for the treatment of patients with advanced germline BRCA1/2-mutated ovarian cancer. Rucaparib (Rubraca) was then approved in 2016 for patients with ovarian cancer with either germline or somatic BRCA1/2 mutations. Approvals for olaparib, niraparib (Zejula), and rucaparib as maintenance therapy followed for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer previously treated with platinum-based chemotherapy. Olaparib has also been approved for the treatment of patients with metastatic germline BRCA1/2-mutant pancreatic cancer. In 2018, the FDA approved olaparib and talazoparib (Talzenna) for treating patients with germline BRCA1/2–mutant, HER2-negative metastatic breast cancer.4

Most recently, 2 PARP inhibitors were approved for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). In May 2020,rucaparib received accelerated approval for treating patients with mCRPC with a deleterious germline or somatic BRCA4 mutation who have received androgen receptor–directed therapy and taxane-based chemotherapy.

The decision was based on the single-arm, phase 2 TRITON2 trial (NCT02952534), in which rucaparib demonstrated an objective response rate (ORR) of 43.5% (95% CI, 31.0%-56.7%) and a rate of prostate-specific antigen (PSA) response (≥50% decrease from baseline) of 54.8% (95% CI, 45.2%-64.1%) among 115 patients with mCRPC harboring BRCA1/2 alterations.2,4 Full FDA approval is contingent on clinical benefit in results from the ongoing phase 3 TRITON3 trial (NCT02979594), which is expected to be complete in spring 2022.

Olaparib was approved just days later for patients with mCRPC previously treated with androgen receptor–directed therapy whose tumors harbor mutations in any of 14 HRR-related genes, including BRCA1/2. The decision was based on the results of the randomized, phase 3 PROfound study (NCT02987543), in which the agent improved progression-free (PFS) and overall survival (OS) compared with enzalutamide (Xtandi) or abiraterone acetate (Zytiga).7,10

**DIFFERENTIAL SENSITIVITY TO PARP INHIBITORS?**
Currently, BRCA1 and BRCA2 mutations are considered as a single entity for the purpose of determining eligibility for PARP inhibitor therapy. Interestingly, exploratory subgroup analyses of TRITON2 data demonstrated that rucaparib elicited a numerically higher PSA response rate in men with mutant BRCA2 vs the BRCA1-mutant subgroup.

The PSA response rate for patients with BRCA1 mutations was 15.4% (2 of 13 patients; 95% CI, 1.9%-45.4%) and 59.8% (61 of 102 patients; 95% CI, 49.6%-69.4%) for those with BRCA2 mutations. There was no difference in ORR between the BRCA1-mutant and BRCA2-mutant subgroups.8

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**BRCA1 vs BRCA2 Mutations**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Mutation Frequency</th>
<th>Differences in Therapeutic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>7.82% VS 6.25%</td>
<td>Improved outcome with PARP inhibitors with BRCA2 vs BRCA1 mutation</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3.12% VS 4.48%</td>
<td>Taxane data conflict for BRCA1, NE for BRCA2</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1.24% VS 6.61%</td>
<td>Improved outcome with PARP inhibitors with BRCA2 vs BRCA1 mutation</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2.0% VS 5.19%</td>
<td>Improved outcome with PARP inhibitors with BRCA2 vs BRCA1 mutation</td>
</tr>
</tbody>
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**NE, not established.**

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Similarly, a more pronounced trend toward improved median OS and PFS was observed in the BRCA2-mutant population in the PROfound study. The median OS in the olaparib-treated arm was 11.7 months for a hazard ratio of 0.42 (95% CI, 0.12-1.53) for patients with BRCA1 mutations and 24.8 months for a hazard ratio of 0.59 (95% CI, 0.37-0.95) for those with BRCA2 mutations. The PFS benefit was lower for patients with BRCA1 mutations (HR, 0.41; 95% CI, 0.13-1.39) than for those with BRCA2 mutations (HR, 0.21; 95% CI, 0.13-0.32).3 As in the TRITON2 study, there were far fewer participants with BRCA1 mutations than BRCA2 (8 vs 81 patients, respectively).

In an editorial accompanying the TRITON2 results, investigators suggested that this differential sensitivity to PARP inhibitors in BRCA1-mutated mCRPC appears to be a class effect. Greater clinical benefit in BRCA2-mutant disease was observed across studies of various PARP inhibitors (rucaparib, olaparib, and talazoparib) in this setting.7 The trend was further explored in a multicenter, retrospective analysis of PARP inhibitor therapy (olaparib, n = 116; rucaparib, n = 3; talazoparib, n = 2; and veliparib, n = 2) for mCRPC that included 13 patients with BRCA1 mutations and 110 patients with BRCA2 mutations. Baseline characteristics were broadly similar between the BRCA1 and BRCA2 groups, except that more patients in the BRCA1 group had metastatic disease at diagnosis.

Patients with BRCA1 mutations had significantly fewer PSA responses (23% vs 63%; OR, 0.18; 95% CI, 0.04-0.62; P = .01), numerically shorter PSA PFS (27.1 vs 43.9 weeks; HR, 1.94; 95% CI, 0.92-4.09; P = .08), shorter PFS (43.4 vs 45.4 weeks; HR, 2.08; 95% CI, 0.99-4.40; P = .05), and shorter OS (49.6 vs 104.6 weeks; HR, 3.01; 95% CI, 1.32-6.83; P = .008) compared with the BRCA2 group. With the exception of PSA-PFS, these differences persisted after adjusting for important clinical and genomic variables (including age, Gleason score, stage, baseline PSA, and previous taxane treatment, as well as concurrent mutations in TP53 or PTEN).8

Several hypotheses regarding the differential sensitivity of BRCA1-mutant and BRCA2-mutant mCRPC to PARP inhibitors have been put forward. One is based on the finding, in the aforementioned retrospective analysis and other prostate cancer studies, that BRCA1 mutations are less likely to be biallelic compared with BRCA2 alterations. The presence of 1 functional copy of BRCA1/2 makes HRD much less likely; accordingly, sensitivity to PARP inhibitors is less common in BRCA1-mutant tumors.5

Another potential explanation is that, compared with BRCA2 mutants, BRCA1-altered mCRPC has a higher prevalence of concurrent mutations in the TP53 gene. In patients treated with PARP inhibitor therapy, TP53 mutations have been shown to allow increased emergence of BRCA2 reversion mutations, which restore the wild-type open reading frame and are associated with acquired resistance to PARP inhibitors.6

Although evidence is currently limited, there is also a suggestion of a differential sensitivity to PARP inhibitors in ovarian and pancreatic cancers with BRCA1 mutations compared with BRCA2 mutations.10,19

**BRCA1 vs BRCA2**

These results highlight the growing appreciation of the distinct biology underlying BRCA1-mutant and BRCA2-mutant cancers and the potential implications for the types of tumors they drive, patient prognosis, and therapeutic response.

Despite their shared name, similar disease phenotype, and functional link to the HRR pathway, BRCA1 and BRCA2 have little else in common. The genes have no homology in their coding regions, and the proteins have different functional domains. The BRCA1 protein has a RING domain with ubiquitin ligase activity and a BRCT domain that mediates binding to phosphoproteins, enabling it to form a variety of multiprotein complexes. This reflects the multifunctional role of BRCA1 beyond HRR.1,2,15,20

The BRCA2 protein, meanwhile, contains a DNA-binding domain and a group of 8 repeats approximately 35 amino acids in length in the region encoded by exon 11. These BRCA2 repeats mediate binding to the RAD51 protein.21,22 BRCA2 appears to function almost exclusively in the HRR pathway.1,2,15,20

In addition to functional differences, there are other distinct aspects of BRCA1-mutant and BRCA2-mutant cancers. In breast cancer, certain molecular subtypes occur at different rates in BRCA1-mutant vs BRCA2-mutant tumors. The former is more commonly associated with the basal-like subtype of breast cancer and is often triple negative for estrogen receptor, progesterone receptor, and HER2 expression, whereas hormone receptor expression is much more common in BRCA2-mutant cancers, which tend to be of the luminal B subtype.20,23

Compared with wild-type tumors, BRCA1/2 mutations yield higher-grade breast tumors in general; however, there is evidence that BRCA1-mutant tumors tend to be higher grade than BRCA2-mutant tumors.24 By contrast, BRCA1-mutant and BRCA2-mutant ovarian cancers do not seem to display significant differences in tumor histology; both are most likely to be high-grade serous tumors.15

In ovarian cancer, BRCA1/2 mutations appear to confer improved PFS and OS compared with the wild-type genes. Preliminary studies suggest that this effect may be more pronounced in BRCA2 mutation carriers and that the prolonged OS observed with BRCA1 mutations may be limited to 5 years, whereas BRCA2 mutations confer improved long-term survival.15

The jury is still out on the prognostic role of BRCA1/2 mutations in breast cancer, with studies producing conflicting results.24,25 In prostate cancer, however, both BRCA1 and BRCA2 mutations correlate with higher Gleason score, nodal involvement, metastatic disease at diagnosis, and T3/4 stage, whereas only BRCA2 mutations confer shorter cancer-specific survival.16

Broadly speaking, BRCA1-mutant cancers are more sensitive to DNA-damaging chemotherapy than their wild-type counterparts.1,16,17,24 However, studies have also begun to tease apart some differences in these effects. Accumulating evidence suggests that BRCA2-mutant ovarian cancer exhibits superior sensitivity to primary platinum-based chemotherapy, as well as a longer platinum-free interval, compared with BRCA1-mutant disease. In fact, mutations at different sites within the BRCA1 gene may affect platinum sensitivity, with studies suggesting that exon 11 mutations may mediate resistance.17

For a full list of references, see the article at OncLive.com.
**TO PROTECT GENOME INTEGRITY**, cells have evolved a complex network of signaling pathways whose members detect and respond to DNA-damaging assaults that can arise both from within the cell (eg, metabolic byproducts, DNA replication errors) and from the external environment (eg, ionizing radiation, chemical agents, UV light).1-3

Known collectively as the DNA damage response (DDR), these processes entail the coordinated action of myriad components of these pathways: sensor, effector, and mediator proteins that recognize DNA damage, regulate the cell cycle (temporarily pausing it to allow damage to be repaired), and execute DNA repair or, if the damage is irreparable, initiate cell death.1,2

A whole host of repair pathways exist to handle various types of DNA damage. The most significant threat to genome integrity is double-strand breaks (DSBs), in which damage affects both strands of the DNA helix.1-3

Without an undamaged DNA strand to serve as a template for repair, the cell is forced to use highly error-prone mechanisms to resolve DSBs. However, during the S and G2 phases of the cell cycle, an intact sister chromatid is accessible and can be used in the mostly error-free homologous recombination repair (HRR) pathway.1-3

HRR involves several main steps, in which the BRCA1 and BRCA2 breast cancer susceptibility proteins (FIGURE1) play key roles. The first step, resection of the damaged double-stranded DNA, is dependent on the activity of the MRN complex (comprising the MRE11, RAD50, and NBS1 proteins). The MRN complex detects the DSB and recruits BRCA1 to the site, where these proteins promote resection. Replication protein A (RPA) binds to the resulting single-stranded DNA ends to protect them from degradation.1,4

BRCA1 also plays a role in the next step, recruitment of the RAD51 recombinase, by binding the bridging protein PALB2, which in turns binds BRCA2. As part of the BRCA1-PALB2-BRCA2 complex, BRCA2 binds RAD51, recruiting it to the site of repair. BRCA2 then simultaneously removes RPA from the ssDNA and loads RAD51 in its place, mediating formation of a nucleoprotein filament consisting of ssDNA and RAD51. This filament searches the sister chromatid for a homologous DNA template.1,4

In the final step of HRR, RAD51 dissociates from the DNA and DSB repair is completed through polymerase-mediated synthesis of the correct DNA sequence using the homologous template. The newly elongated DNA is reconnected to the rest of the DNA molecule by ligases.1,2,4

Because unrepaired DNA fosters the genomic instability that is a major driving force of oncogenic transformation, defects in DDR pathways or other components of the DDR are common across a variety of cancer types. Many of the constituent proteins of the DDR, including BRCA1/2, act as tumor suppressors. A germline mutation in a single allele of the genes that encode these proteins can significantly enhance a patient’s cancer risk, with somatic loss of the remaining wild-type allele typically triggering tumorigenesis.2,4

**REFERENCES**

UKONIQ is indicated for the treatment of adult patients with:

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

**THE POWER**

Relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen

**IMPORTANT SAFETY INFORMATION**

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

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

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

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

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

**POWERFUL EFFICACY IN R/R MZL AND FL WITH SINGLE-AGENT UKONIQ**

**2 PATHWAYS, 1 FOCUS.**

**UKONIQ: THE FIRST AND ONLY TARGETED KINASE INHIBITOR OF PI3K-DELTA AND CK1-EPSILON**

UKONIQ was evaluated in an open-label, multi-cohort, single-arm study in 69 patients with MZL who received at least 1 prior therapy (including an anti-CD20 regimen) and 117 patients with FL who received at least 2 prior systemic therapies (including an anti-CD20 monoclonal antibody and an alkylating agent). The trial excluded patients with Grade 3b FL, large-cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Efficacy was based on ORR as assessed by an IRC using criteria adopted from the IWG for malignant lymphoma.

Limitations: The study was not powered to determine efficacy based on disease control rate. It is not possible to determine if stable disease is experienced as a result of the natural progression of disease or treatment with UKONIQ.

Please visit UKONIQ.COM for additional safety information.
These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

UKONIQ is indicated for the treatment of adult patients with:

**IMPORTANT SAFETY INFORMATION**

at least every 2 weeks for the first 2 months of UKONIQ and at least monthly. Grade 3 neutropenia developed in 9% of 335 patients and Neutropenia:

monitor patients for CMV reactivation by PCR or antigen test at UKONIQ. Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. If pneumonia (PJP) and consider prophylactic antivirals during treatment frequent Grade ≥3 infections included pneumonia, sepsis, and Serious, including fatal, infections occurred in patients neutropenia during treatment with UKONIQ. Consider supportive Serious hepatotoxicity occurred in patients treated of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis. Any grade diarrhea change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric

Diarrhea or Non-Infectious Colitis:

Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash any adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

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

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

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


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06/2021 US-UMB-2000079

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UKONIQ® (umbralisib) tablets, for oral use
This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

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

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

2. CONTRAINDICATIONS
None.

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

Monitor for any new or worsening signs or symptoms of infections. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose (see Dosage and Administration [2.3]).

Provide prophylaxis for Pneumocystis jirovecii pneumonia (PJP) during treatment with UKONIQ (see Dosage and Administration [2.2]). Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP (see Dosage and Administration [2.3]).

Monitor for cytomegalovirus (CMV) infection during treatment with UKONIQ in patients with a history of CMV infection. Consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation (see Dosage and Administration [2.2]). For clinical CMV infection or virologic viral shedding, suspend UKONIQ until infection or viroemia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly (see Dosage and Administration [2.2]).

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

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

For patients with severe diarrhea (Grade 3, i.e., >6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis (see Dosage and Administration [2.3]).

5.4. Hepatotoxicity
Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 325 patients (see Adverse Reactions [6.1]). The median time to onset for Grade 3 or higher transaminase elevations was 2.2 months (range: 15 days to 4.7 months).

Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ (see Dosage and Administration [2.3]).

5.5. Severe Cutaneous Reactions
Serious cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily macular-papular) (see Adverse Reactions [6.1]). The median time to onset of Grade 3 or higher cutaneous reaction was 15 days (range: 9 days to 6.4 months). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade (see Dosage and Administration [2.3]). Provide supportive care as appropriate.

5.6. Allergic Reactions Due to Inactive Ingredient FDBc Yellow No. 5 (UKONIQ contains FDBc Yellow No. 5 [tartrazine], which may cause allergic-type reactions including bronchial asthma in certain susceptible persons. Although the overall incidence of FDBc Yellow No. 5 [tartrazine] sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

5.7. Embryo Fetal Toxicity
Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of umbralisib to pregnant mice during the period of organogenesis caused adverse developmental outcomes including embryo-fetal mortality and fetal malformations at maternal exposures comparable to those in patients at the recommended dose of 800 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for one month 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:

- Infections (see Warnings and Precautions [5.1])
- Neutropenia (see Warnings and Precautions [5.2])
- Diarrhea and Non-infectious Colitis (see Warnings and Precautions [5.3])
- Hepatotoxicity (see Warnings and Precautions [5.4])
- Severe Cutaneous Reactions (see Warnings and Precautions [5.5])

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 compared to rates in the clinical trials of another drug and may not reflect the rates observed in the general patient population.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to UKONIQ as monotherapy at a dosage of 800 mg orally once daily in 335 adults with hematologic malignancies who received up to 12 cycles of UKONIQ (TGR-1202, TGR-205, and TGR-501). Among these 335 patients who received UKONIQ, 52% were exposed for 6 months or longer and 30% were exposed for greater than one year.

Relapsed or Refractory Follicular Lymphoma and Marginal Zone Lymphoma
The safety of UKONIQ was evaluated in a pooled safety population that included 221 adults with marginal zone lymphoma (37%) and follicular lymphoma (63%) enrolled in three single-arm, open-label trials (Study TGR-1202-101, TGR-1202-202, and TGR-501) and one open-label extension trial (Study UTX-TGR-301) (see Clinical Studies [7.1, 14.1, 14.2]). These trials required hepatic transaminases ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥30 mL/min. No patients had prior exposure to a PI3K inhibitor. Potent exposure to a PI3K inhibitor was received UKONIQ 800 mg orally once daily. Among these 221 patients who received UKONIQ, 60% were exposed for 6 months or longer and 34% were exposed for greater than one year.

The median age was 66 years (range: 29 to 88 years), 43% were female, and 97% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 92% of patients. These patients had a median of 2 prior therapies (range: 1 to 10). Serious adverse reactions occurred in 18% of patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Fatal adverse reactions occurred in <1% of patients who received UKONIQ, including exfoliative dermatitis.

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

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

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

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

*Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.3 grading system.
8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action [see Clinical Pharmacology (12.1)], UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of umbilasib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and structural abnormalities at maternal exposures (AUC) comparable to those in patients at the recommended dose of 800 mg (see Data). Advise pregnant women 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 an embryo-fetal development study in mice, pregnant animals were administered oral doses of umbilasib at 100, 200, and 400 mg/kg/day during the period of organogenesis. Malformations were observed at doses of 200 mg/kg/day (daily intake and 400 mg/kg/day (daily intake and include folded retina, delayed ossification of sternum and vertebrae, increased resorptions, and increased post-implantation loss. The exposure (AUC) at a dose of 100 mg/kg/day in mice is approximately equivalent to the human exposure at the recommended dose of 800 mg. In an embryo-fetal development study in rabbits, pregnant animals were administered oral doses of umbilasib at 30, 100, and 300 mg/kg/day during the period of organogenesis. Administration at 300 mg/kg/day resulted in maternal toxicity (decreased food consumption and body weight) and reduced fetal weights. The exposure (AUC) at 300 mg/kg/day in rabbits is approximately 0.03 times the exposure in human patients at the recommended dose of 800 mg.

8.2. Lactation

Risk Summary

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

8.3. Females and Males of Reproductive Potential

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

Contraception

Females

Advise female patients of reproductive potential to use highly effective contraception during treatment with UKONIQ and for at least 4 months after the last dose.

Males

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

Infertility

Males

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

8.4. Pediatric Use

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

8.5. Geriatric Use

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

8.6. Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance [Ccr] 30 to 89 mL/min estimated by Cockcroft-Gault equation) [see Clinical Pharmacology (12.3)]. UKONIQ has not been studied in patients with severe renal impairment (Ccr < 20 mL/min).

8.7. Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin < upper limit of normal (ULN) and AST > ULN or total bilirubin > 1 to 1.5 × ULN and any AST) [see Clinical Pharmacology (12.3)]. UKONIQ has not been studied in patients with moderate (total bilirubin > 1.5 x ULN and any AST) or severe hepatic impairment (total bilirubin > 3 x ULN and any AST).

14. CLINICAL STUDIES

14.1. Marginal Zone Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205 (NCT02779358), an open-label, multi-center, multi-cohort trial. Patients with MZL were required to have had at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 69 patients with MZL (extranodal [N=38], nodal [N=20], and splenic [N=11]) were enrolled in this cohort. The median age was 67 years (range: 34 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, 7% were Other, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy.

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>34 (49)</td>
</tr>
<tr>
<td>CR, n(%)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>PR, n(%)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>DDR</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>Range, months</td>
<td>0.0, 21.8</td>
</tr>
</tbody>
</table>

- Denotes censored observation

The median time to response was 2.8 months (range: 1.8 to 21.2 months). Overall response rates were 44.7%, 60.0%, and 45.5% for the 3 MZL sub-types (extranodal, nodal, and splenic, respectively).

14.2. Follicular Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, multi-cohort trial (NCT02779358). Patients with relapsed or refractory FL were required to have received at least two prior systemic therapies, including at least one anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3B FL, large cell transformation, prior autologous transplantation, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 117 patients with FL were enrolled in this cohort. The median age was 65 years (range: 29 to 87 years), 38% were female, 60% were White, 4% were Black, 73% had Stage III-IV disease, 38% had bulky disease and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median of 3 prior lines of therapy (range: 1 to 10), with 36% refractory to their last therapy.

Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.1 months (range: 13.5 to 29.6 months). Efficacy results are shown in Table 6.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>30 (43)</td>
</tr>
<tr>
<td>CR, n(%)</td>
<td>33 (62)</td>
</tr>
<tr>
<td>PR, n(%)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>DDR</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>Range, months</td>
<td>0.0, 20.9</td>
</tr>
</tbody>
</table>

- Denotes censored observation

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

15. PATIENT COUNSELING INFORMATION

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

Infections

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

Neutropenia

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

Diarrhea or Non-infectious Colitis

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

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

Hepatotoxicity

Advises pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)].

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

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

Lactation

Advises women not to breastfeed during treatment with UKONIQ and for one month after the last dose [see Use in Specific Populations (8.2)].

Infertility

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

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

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

Administration

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

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

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Mitigating Toxicities Will Position BCMA for Role in Triple-Class Refractory Multiple Myeloma

by BRITTANY LOVELY

DEFINING PHARMACOLOGIC TREATMENT STRATEGIES for patients with multiple myeloma whose disease becomes refractory to standard-of-care treatment options presents a challenge for investigators. Specifically, efforts to develop treatment strategies for patients whose disease becomes triple-class refractory—failing treatment with proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies—have become a key clinical research priority.

Novel treatment strategies have begun to fill the sparse treatment landscape for this population, adding greater benefit than that seen with standard treatment options including salvage autologous stem cell transplant, chemotherapy, and recycling prior therapeutic regimens. One area of active development is the development of therapeutic regimens targeting B-cell maturation antigen (BCMA). In a recent OncLive Peer Exchange® program, an expert panel of oncologic hematologists discussed the latest developments and future of BCMA in multiple myeloma, which moderator Keith Stewart, MB ChB, MBA, said is “the most exciting area in myeloma research.” In addition to the various strategies making headway in the triple-class refractory setting, the panelists gave their insights on the risk/benefit ratio of the BCMA-targeted therapeutic options, including management of common treatment-related adverse effects (AEs).

BCMA SPARKS THERAPEUTIC DEVELOPMENT

A member of the tumor necrosis factor receptor superfamily, BCMA is highly expressed on malignant plasma cells in patients with multiple myeloma and is notably absent from normal human tissue. Early investigative efforts demonstrated that T cells engineered to target BCMA were able to recognize primary multiple myeloma cells, providing a rationale to explore the target to eradicate residual disease in patients who experience relapse.

Targeting BCMA has shifted the development of chimeric antigen receptor (CAR) T-cell therapies for patients with relapsed or refractory multiple myeloma. In March 2021, the FDA approved the BCMA-directed CAR T-cell therapy idecabtagene vicleucel (ide-cel; Abecma) for the treatment of adult patients with relapsed or refractory multiple myeloma following 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The approval was based on data from the phase 2 KarMMa study (NCT03361748), which enrolled patients who had received at least 3 prior lines of therapy. Results showed that treatment with the cellular therapy demonstrated a favorable benefit-risk profile regardless of the number of prior lines of therapy in this patient population.

Updated data for the 128 patients who received treatment at 150-450 × 10⁶
CAR-positive T cells were presented at the 2021 American Society for Clinical Oncology Annual Meeting. The overall response rate (ORR) was 73%, comprising a complete response rate of 33%, a very good partial response (VGPR) rate of 20%, and a partial response rate of 20%. The median progression-free survival (PFS) for all treated patients was 8.6 months and the median overall survival (OS) was 24.8 months. Among the 94 responders the median duration of response was 10.9 months (95% CI, 9.0-11.4), and 21.5 months (95% CI, 12.5-not estimable) for those who achieved a complete or stringent complete response (sCR). “[Ide-cel] is the first approved product [and] there are others coming down the line,” Nina Shah, MD, said. “We’re hoping to see how we might be able to transition this from a research thing, a boutique [option], to a standard of care, much like our lymphoma colleagues were able to do.”

In terms of safety, an analysis of neurotoxicity from the KarMMA study detailed the incidence of events such as cytokine release syndrome (CRS). In total, 84% of treated patients had at least 1 CRS event, 78% of which were grade 1 or 2; no grade 4 or 5 events occurred. The median time to onset was similar regardless of grade, and investigators reported that patients who experienced neurotoxicity achieved frequent and deep responses with therapy.

According to Cristina Gasparetto, MD, investigators have learned more about CRS and other neurotoxicity events associated with CAR T-cell therapy and, as such, management of them has become routine in the standard of care. “A majority of patients will develop CRS and we have learned how to manage this type of toxicity over the past few years. If you look the toxicity profile, we don’t see a lot of the grade 3 and 4 [events]. It’s more manageable with the tocilizumab [Actemra] intervention,” she said.

Other BCMA-directed CAR T-cell therapies are in development and under review at the FDA, including ciltacabtagene autoleucel (cilta-cel). In results from the 1b/2 CARTITUDE-1 trial (NCT03548207), cilta-cel elicited early, deep, and durable responses with a manageable safety profile in heavily pretreated patients with multiple myeloma. The agent received a priority review designation from the FDA in early 2021.

Specifically, at a median follow-up of 18 months, the ORR was 97.9%, with an sCR rate of 80.4%, a VGPR rate or better of 94.8%, and a partial response rate of 3.1% among 97 treated patients. In terms of safety, 94.8% of patients experienced a CRS event; the median time to onset was 7 days (range, 1-12) and the median duration was 4 days (range, 1-97). Most of these cases were grades 1 or 2 in severity (94.6%) and most were resolved within 14 days of onset (98.9%).

Further, investigators of the phase 2 CARTITUDE-2 study (NCT04133636) evaluated cilta-cel in patients who had received 1 to 3 prior lines of therapy and were refractory to lenalidomide (Revlimid). Among 20 patients who received treatment with a target dose of cilta-cel at 0.75 × 10^6/kg, elicited in an ORR of 95% (95% CI, 75%-100%) was elicited, with an sCR rate of 75% (95% CI, 51%-91%) and a VGPR rate or better of 85% (95% CI, 62%-97%). The median time to CRS onset was 7 days (range, 5-9) and the incidence of neurotoxicity was 20%, with all events reported at grade 1 or 2. Although the process of cellular therapy remains long, [and involves] a patient having their T cells collected and weeks to do manufacturing, it’s becoming considerably safer,” Joseph Mikhael, MD, said. "Fortunately, I remember some of the earliest CAR T trials in myeloma, where a significant fraction of patients had real, very significant toxicity and even death. We have groups around the world now that are convening to enhance our management of CRS, of the neurological toxicities that can emerge,” he said.

An emerging BCMA-directed allogeneic CAR T-cell therapy, ALLO-715, has demonstrated activity in data from the phase 1 UNIVERSAL study (NCT04093596) and may provide a faster and safer course of treatment for patients with triple-refractory disease. The “off-the-shelf” product administered at a dose of 320 × 10^6 CAR cells dose plus an ALLO-647 lymphodepletion regimen elicited an ORR of 60% (95% CI, 14.7%-94.7%) among 10 patients. This included a VGPR rate or better in 40% of patients. In August, the FDA granted an orphan drug designation to ALLO-715.

BCMA MONOCLONAL ANTIBODIES

In August 2020, the FDA granted accelerated approval to the BCMA-targeted monoclonal antibody belantamab mafodotin-blmf (Blenrep) for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies. These include an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

The approval was based on results of the phase 2 DREAMM 2 trial (NCT03525678). The agent administered intravenously once every 3 weeks at a dose of 2.5 mg/kg, elicited an ORR of 31% (95% CI, 21%-43%) among 97 treated patients.

In a 13-month follow-up of the trial, investigators reported that 32% (97.5% CI, 21.7%-43.6%) of patients had achieved an overall response and that previously reported responses deepened over time in some patients. Specifically, 12 responders who initially had a partial response or better subsequently experienced a deeper response to treatment.

Of the 31 responders, 58% had achieved a VGPR or better with 7 patients having an sCR or a complete response. A minimal response or better was reported in 35 of 97 patients for a clinical benefit of 36%. Patients received a median of 3 treatment cycles (range, 1-17). The median PFS was 2.8 months (95% CI, 1.6-3.6) and the median OS was 13.7 months (95% CI, 9.9-not reached), with an estimated 1-year survival probability of 58% (95% CI, 47%-67%).

In terms of safety, the panel elucidated the ocular toxicities associated with the agent, specifically those included in the box warning for corneal epithelium. These may result in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes. In the updated analysis, investigators reported that 68
patients experienced keratopathy and that the first reported finding was by treatment cycle 4 for 66 patients. The median time to onset of the first keratopathy was 37 days (range, 19-143). Data for 60 patients were available in the analysis, which showed that 77% of patients who experienced grade 2 or higher keratopathy recovered to baseline and 48% recovered from their last event. The median time to recovery from the first examination finding was 86.5 days (range, 8-358).

“The full mechanism of belantamab mafodotin is still to be elucidated,” Mikhael said. “We think [ocular toxicity] has to do with the conjugate that is part of the drug; it has the BCMA antibody and that toxin gets dropped in and incorporated into the cell.”

Prior to receiving treatment, Mikhael noted that “what [patients must do] at baseline before their first dose, and before the doses are scheduled every 3 weeks, [is] see either an ophthalmologist or an optometrist, an eye specialist, to do 2 things: check their visual acuity and [undergo] the slit lamp exam to look for evidence of keratopathy. And if they have grade 1 keratopathy or below, we can proceed [with treatment].” He added that if keratopathy worsens there must be a delay in the treatment. “It’s a bit of a logistical challenge, but feasible and doable, and a significant fraction of individuals who had to delay doses because of keratopathy were still able to continue therapy.”

Gasparetto agreed, noting that she does not feel comfortable proceeding with the agent without an ophthalmology exam. Even with dose reductions or interruptions the agent appears to be effective. “I like the fact that the majority of the responders, even if they miss a few doses, maintain the response,” she said. “That was very interesting, and what I think is going to be the key [in] mitigating the toxicity.”

Just as with CAR therapy, Mikhael added, “We’re getting more and more familiar using these agents and we will optimize them with time. I personally, without going out too far on the limb, think that the dosing of this drug may be more effective less frequently, and patients will potentially have less keratopathy, but we have to do the studies to show that.”
PARSING A CROWDED LANDSCAPE

As more agents enter the treatment landscape and testing patients for BCMA becomes a standard practice, deciding between available therapies presents a new challenge. Stewart asked the panel which treatment, given the choice between the 2 approved therapies, would they recommend for a patient who is triple-class refractory—belantamab mafodotin or ide-cel.

Mikhael said he would discuss the options with patients and that understanding their preference as well as the safety considerations for each therapy would play a role in the process (FIGURE 4-13). “To me, you sort of go through the potential risks and benefits of each of the 2 treatments and lay them out for the patient,” he said. “There are patients who say, ‘I don’t want to go in the hospital for whatever you’re going to do to me,’ and that takes CAR T-cell therapy off the table. You describe CRS to them, even though it’s mild in most patients, and they don’t want to be put at risk. Then there are other patients for whom any concern about loss of the ability to read or to drive is a deal breaker. For them, [belantamab mafodotin] is not necessarily going to be the right answer either.”

Shah agreed, adding that she prefers to offer CAR T-cell therapy to these patients, but that support systems and the opportunity to present a patient with this option play a role in the decision-making process. “If the patient has support and desires to come to the center, I would pick CAR T-cell therapy because it’s a ‘1 and done’ treatment and does have a higher ORR and, at this time, a higher PFS,” she said.

CAR therapies and belantamab mafodotin are 2 options facing scrutiny in practice; however, another method of targeting BCMA is under active investigation in the trials. Bispecific T-cell engagers (BiTEs) are engineered to target BCMA and CD3, redirecting T cells to multiple myeloma cells (TABLE).15-17 Early response data for heavily pretreated patients are promising, and Gasparetto said it will be “interesting over the next year or so to see how we can sequence these agents.”

Stewart noted that BiTEs may present a unique opportunity for patients for whom CAR therapy is either not available or for whom treatment presents a logistical challenge. “[Data for the] 4 or 5 patients are very impressive and they’ve all got a 60% to 70% response rate; it’s hard to tell the difference between them,” he said. “If I was in the community, this is attractive. I can probably treat [them] in my local hospital for a couple of days to watch for CRS and then treat these patients at home. Why would I [send them] to get CAR T-cell therapy if I have these [agents] available?”

Shah said that in the hypothetical scenario she would still prefer that a patient undergo CAR T-cell therapy; however, each patient presents a unique case and should be assessed based on their fitness, age, comorbidities, and prior therapies. “Not all myeloma patients are the same; as I always say, there’s enough myeloma to go around,” Shah said. “If [CAR therapy] is not possible, then I think bispecifics are a reasonable option.”

“BCMA therapies are here to stay,” Stewart concluded. “They’re very exciting and I think they’re going to really create a paradigm shift in how we treat myeloma. For example, I wouldn’t be surprised if BiTEs targeting BCMA become part of our frontline regimens in the not-too-distant future. For now, these are still in clinical trials, but I think many of your academic centers will have these available.”

REFERENCES

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